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Investigation of Selected Potential Environmental Contaminants
Epichlorohydrin and Epibromohydrin

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16. ABSTRACT

This report reviews the potential environmental and health hazards associated with the commercial use of epichlorohydrin and epibromohydrin. Epichlorohydrin is used primarily as a chemical intermediate in the production of glycerin and epoxy resins, with small amounts exported or used for elastomers or other products. Epibromohydrin was last produced on a commercial scale in 1975; the only current use of epibromohydrin appears to be as a laboratory research reagent. Information on physical and chemical properties, production methods and quantities, commercial uses and factors affecting environmental contamination, as well as information related to health and biological effects, are reviewed and evaluated.

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INVESTIGATION OF SELECTED POTENTIAL ENVIRONMENTAL CONTAMINANTS:

EPICHLOROHYDRIN AND EPIBROMOHYDRIN

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EXECUTIVE SUMMARY

Epichlorohydrin (ECH) is produced in about 400 million lbs per year. It is produced by two companies (Dow and Shell) at three sites. ECH is primarily used as a chemical intermediate in the production of glycerin and epoxy resins, with small amounts exported or used for elastomers or other products. Epibromohydrin (EBH) was last produced on a commercial scale in 1975 when a batch of 20,000 lbs was manufactured. Substantial amounts of ECH and other chlorinated organics are released in air effluents or have to be disposed of during production of ECH. One estimate suggests that approximately 600,000 lbs/per year of ECH are released in atmospheric venting. A recent derailment and rupture of a tank car of ECH resulted in the release of 20,000 gallons of ECH, evacuation of 400 people, and the closing of a public water supply plant.

Almost no U.S. effluent monitoring data and no ambient monitoring data on ECH are available, although Russian studies have detected ECH in air samples near factories and in structures where epoxy resins and plastics were used. ECH hydrolysis occurs in water with a half-life of 4-8 days. Under smog conditions, its half-life in the atmosphere is 16 hrs but its reactivity under less polluted conditions is unknown.

Investigations of the biological effects produced by contact with ECH were begun several decades ago. Animal studies and case reports from occupational exposures have clearly shown that ECH is irritating to the eyes, skin, and respiratory tract.

Systematic studies of ECH-exposed worker populations have recently revealed the presence of chromosome abnormalities in certain blood cells. The

significance of these changes is not known, but they may indicate a potential increase in carcinogenic and/or mutagenic risk from ECH absorption. One epidemiologic investigation of 864 active and retired workers exposed to ECH has shown an excess incidence of death due to cancer of respiratory organs. Deficiencies in the available data base prevent the formulation of definitive conclusions, but nevertheless the results were interpreted to indicate a possible carcinogenic threat by ECH in occupational situations. There are no confirming data in human populations, however, regarding ECH as a carcinogen.

Preliminary results from animal bioassays with ECH are now available which demonstrate a carcinogenic effect from inhalation exposures to rats. Using various concentrations and treatment schedules, ECH induced squamous cell carcinomas of the nasal cavity in certain animals. This type of tumor is very rare in rats, and thus clearly appeared to be treatment-related. The potential carcinogenicity of ECH is further supported by the results of mutagenicity assays with bacteria.

It is not clear whether current levels of ECH in the environment pose a threat to public health. Likewise, there is at present an insufficient data base to predict any ecological effects due to ECH contamination. However, extrapolations from animal bioassay data and studies in worker populations lead to the conclusion that ECH may pose a carcinogenic threat to man. The magnitude of any potential threat is presently unquantified.

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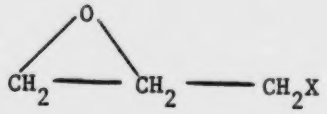
I. Physical and Chemical Data

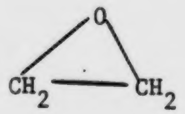
A. Structure and Properties

1. Chemical Structure and Nomenclature

Epihalohydrins are γ-halogenated derivatives of α,β-propylene oxide:



In this review, X is either chloride or bromide; they are commonly known as epichlorohydrin and epibromohydrin, respectively. The IUPAC system names them as derivatives of oxirane (which is commonly known as ethylene oxide):



Thus, epichlorohydrin and epibromohydrin are listed as chloromethyloxirane and bromomethyloxirane, respectively, by the IUPAC system. Table 1 lists other common names and the CAS Registry Numbers. Throughout this report, the names "epichlorohydrin" and "epibromohydrin," or abbreviations "ECH" and "EBH," respectively, will be used.

2. Physical Properties of the Pure Material

Table 2 summarizes the major physical properties of ECH and EBH. Both are colorless liquids at room temperature with irritating chloroformlike odors. ECH is slightly volatile and water soluble. EBH is denser, higher boiling, and less water soluble (Weast, 1975). Both form azeotropes with water and also with organic liquids (Prager and Jacobson, 1933). The ECH water

Table 1. Structure and Nomenclature of Epichlorohydrin and Epibromohydrin

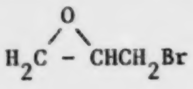
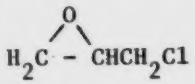
Molecular Structure	CAS Number	IUPAC Name	Common Names
 $H_2C(O)-CHCH_2Br$	3132-64-7	bromomethyloxirane	epibromohydrin 1-bromo-2,3-epoxypropane
 $H_2C(O)-CHCH_2Cl$	106-89-8	chloromethyloxirane	epichlorohydrin 1-chloro-2,3-epoxypropane 3-chloro-1,2-epoxypropane (chloromethyl)ethylene oxide 2-(chloromethyl) oxirane chloropropylene oxide γ-chloropropylene oxide 3-chloro-1,2-propylene oxide α-epichlorohydrin (DL)-α-epichlorohydrin 1,2-epoxy-3-chloropropane 2,3-epoxypropyl chloride

Table 2. Physical Properties of Epichlorohydrin and Epibromohydrin[1-6]

	Epichlorohydrin	Epibromohydrin
Molecular weight	92.53	136.98
Color	none	none
State at STP	liquid	liquid
Boiling point	116.2°C (760 mm); 47.4-48.4°C (70 mm)	138-140°C (760 mm); 63-64.4°C (60 mm)
Melting point	-57.2°C[4]	-40°C
Density	d_4^{20}1.1812; d_4^{25}1.1750	d_{25}^{25}1.663
Refractive index	n_D^{25}1.4359	n_D^{23}1.4780
Vapor pressure	79.8 torr (55.2°C)	----
Viscosity	0.9116 g/cm-sec (29°C)	0.92 centistokes (25°C)
Solubility		
Water (weight percent)	6.52 (10°C); 6.58 (20°C)	insoluble
Ethanol	soluble	soluble (hot)
Diethyl ether	soluble	soluble
Acetone	soluble	----
Chlorinated aliphatic hydrocarbons	soluble	soluble
Pentroleum hydrocarbons	soluble	----
Benzene	soluble	soluble

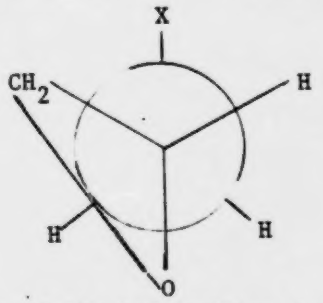
---

[1] IARC, 1976
[2] Weast, 1975
[3] NIOSH, 1976
[4] Shell, 1969
[5] Prager and Jacobsen, 1933
[6] Great Lakes Chemical Corp., 1975

azeotrope distills at 86° and contains 75% epichlorohydrin by weight (Lichtenwalter and Riesser, 1964).

No ultraviolet spectra were available for the two compounds. Based upon the epihalohydrin structure (which combines alkyl halide and alkyl epoxide), it is reasonable to infer that absorption maxima will be below 300 nm, which is the cutoff for sunlight. The tail of the EBH absorption peak might extend above the 300 nm region (Calvert and Pitts, 1966).

Electron diffraction studies on EBH by Igarachi (1961) showed that the bromine atom favors trans orientation to the oxirane ring. Thus, it appears that the epihalohydrins favor the rotameric structure:



The β-carbon of the halohydrins is asymmetric and the enantiomers have been isolated. Optical activity has been reported as $[\alpha]_D^{18} = -25.6°$ for the levorotatory enantiomer of ECH and $[\alpha]_D^{18} = +23.1°$ for dextrorotatory. Enantiomers of both halohydrins are racemized by distillation at atmospheric pressure (Prager and Jacobson, 1933).

3. Properties of Commercial Material

Commercial refined grade epichlorohydrin is a high-purity material (ca. 99%) with properties as described previously for the pure material. The sales specifications for refined epichlorohydrin are as follows (Shell, 1970):

Purity, % weight, min.	99.0
Specific Gravity, 20/20°C	1.181-1.184
Water, % weight, max.	0.10
Color, APHA, max.	15
Distillation Range	
Initial BP, min.	113°C
Distillation Range, max.	118°C

Specific sales specifications for crude ECH are not available because practically all of it is used captively either to make glycerin or refined ECH for epoxy resins. The properties of the crude no doubt differ from the specifications above in relation to the impurities present in the particular batch.

Commercial specifications for EBH are not available from the Great Lakes Chemical Corporation, the sole U.S. manufacturer, which claims it is produced only occasionally in small batches on special order.

4. Principal Contaminants of the Commercial Product

Epichlorohydrin is prepared commercially by a sequence of reactions: propene and chlorine are reacted to form allyl chloride; allyl chloride is reacted with hypochlorous acid to form dichlorohydrins; and the dichlorohydrins are reacted with sodium hydroxide or calcium hydroxide to form ECH (Oosterhof, 1975). The reactions are described in Section II-A-3. The major by-products are:

cis- and *trans*- 1,3-dichloropropene
1,2-dichloropropene
1,2,3-trichloropropane
Dichloropropanols
Chlorinated ethers
Chlorinated, saturated, and unsaturated short-chained aliphatic hydrocarbons

All of these chemicals are potential contaminants of the final product. They are rated as moderately toxic (Gruber, 1976).

The dichloropropenes are commercially useful as nematocides. Dow Chemical and Shell Chemical recover them and they are marketed under the tradenames "Telone" and "D-D," respectively. The active ingredient is 1,3-dichloropropene, which accounts for approximately 50-60% (by weight) of the commercial nematocide (Oosterhof, 1975).

The refined, commercial epichlorohydrin is specified as 99% pure (see Section I-A-3) which can include as much as 0.1% water. The composition of the organic contaminant was not available.

No information was available concerning the principal contaminants of commercial epibromohydrin.

B. Chemical Reactions in the Environment

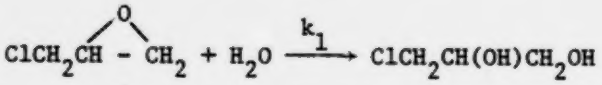
While available literature provides a good description of hydrolysis and related reactions of the epichlorohydrins, little information was available on their photochemistry or oxidation in environmentally significant conditions. The epihalohydrins are not persistent and appear to hydrolyze in several weeks' time. No field studies on the epihalohydrins were found in the literature.

1. Hydrolysis and Related Reactions

The epihalohydrins hydrolyze by a complex scheme. Although most of the studies have investigated only ECH, based upon limited available literature EBH does appear to hydrolyze by the same scheme and probably at slightly faster rates. Virtually all the published information has attempted to delineate mechanisms and rates of epoxide hydrolysis. Although none of the studies have investigated hydrolysis at environmental conditions, the large quantity of excellent data permits insight into expected hydrolysis rates and products in the ambient environment.

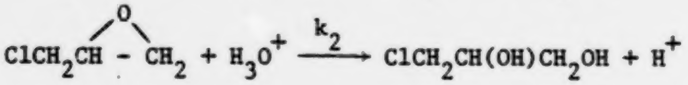
The literature concensus is that ECH hydrolyzes as expected of a derivative of 1,2-propene oxide. The chlorine atom does not react or directly participate in initial hydrolysis, but it does affect the initial hydrolysis rate by its inductive and electronic effects (Ross, 1950, 1962; Pr[illegible] and Long, 1956; Pritchard and Siddiqui, 1973; Kwart and Goodman, 1960).

ECH, as well as other 1,2-propene oxides, hydrolyzes by four pathways (Brönsted *et al.*, 1929; Ross, 1950):



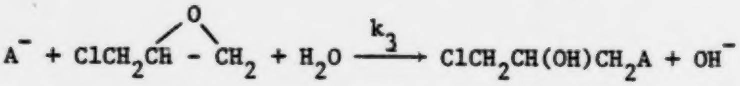
$$ClCH_2\overset{O}{CH - CH_2} + H_2O \xrightarrow{k_1} ClCH_2CH(OH)CH_2OH$$

Reaction 1



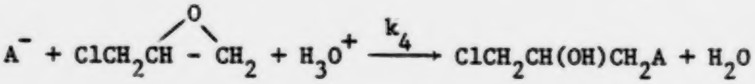
$$ClCH_2\overset{O}{CH - CH_2} + H_3O^+ \xrightarrow{k_2} ClCH_2CH(OH)CH_2OH + H^+$$

Reaction 2



$$A^- + ClCH_2\overset{O}{CH - CH_2} + H_2O \xrightarrow{k_3} ClCH_2CH(OH)CH_2A + OH^-$$

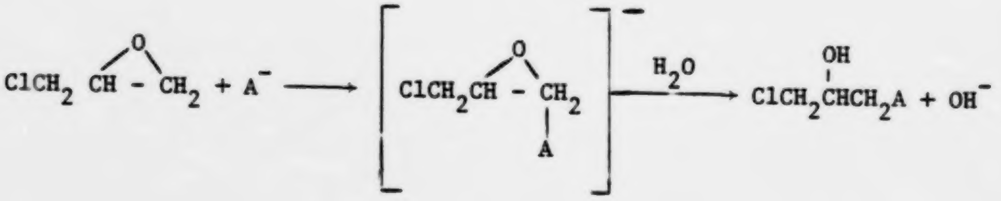
Reaction 3



$$A^- + ClCH_2\overset{O}{CH - CH_2} + H_3O^+ \xrightarrow{k_4} ClCH_2CH(OH)CH_2A + H_2O$$

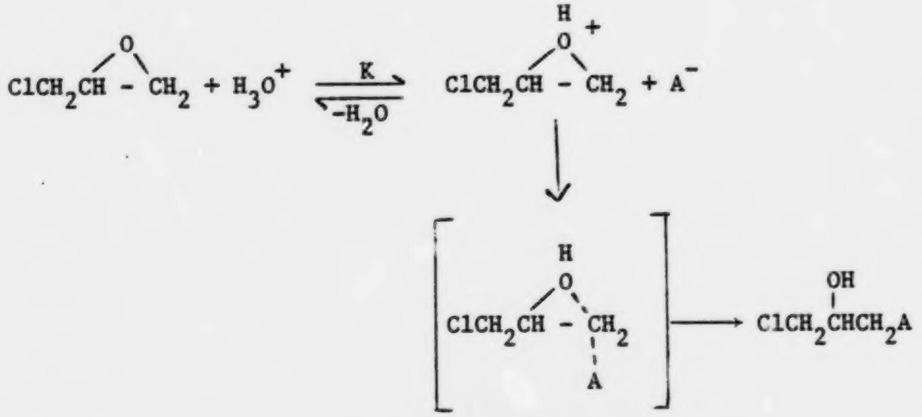
Reaction 4

The reaction mechanisms are similar for the uncatalyzed (Reactions 1 and 3) and acid-catalyzed (Reactions 2 and 4) hydrolyses. In uncatalyzed reactions, either water or anion opens the epoxide by attack at C-1 in the rate determining step (Brönsted *et al.*, 1929; Kwart and Goodman, 1960; Long and Pritchard, 1956; Addy and Parker, 1965):



$$ClCH_2\ \overset{O}{CH - CH_2} + A^- \longrightarrow \left[ClCH_2\overset{O}{CH - \underset{A}{CH_2}} \right]^- \xrightarrow{H_2O} ClCH_2\overset{OH}{C}HCH_2A + OH^-$$

The acid catalyzed reactions have been identified as an A-2 mechanism. ECH is protonated reversibly, then the protonated ECH reacts with water or anion. Ring opening again occurs at C-1 in the rate determining step (Brönsted et al., 1929; Long and Pritchard, 1956; le Noble and Duffy, 1964):



Hydrolysis rate equations are:

Rate for Reaction 1 = $k_1\ C_{ECH}$ Equation 1

Rate for Reaction 2 = $k_2\ C_{ECH}\ C_{H_3O^+}$ Equation 2

Rate for Reaction 3 = $k_3\ C_{ECH}\ C_A$ Equation 3

Rate for Reaction 4 = $k_4\ C_{ECH}\ C_A\ C_{H_3O^+}$ Equation 4

These rate equations can be applied to calculate the half-life for chemical hydrolysis of ECH in the environment and to estimate hydrolysis products. This estimate represents only the initial product formation, since some hydrolysis products can further react (see below). These calculations require the identification and quantitation of the reactive anions (including halides, carbonates, and carboxylates) in solution and rate constants for each reaction (at the proper temperatures). The ionic strength also is a factor (Brönsted et al., 1929; Petty and Nichols, 1954), but is minor and not being considered in this discussion. The reaction between ECH and water, which yields 3-chloro-1,2-propanediol (CPP), has the rate expression:

$$\frac{dC_{CPP}}{dt} = (k_1 + k_2\, C_{H_3O^+})C_{ECH} \qquad \text{Equation 5}$$

The reaction between ECH and each anion, A_i, will yield 1-substituted-3-chloro-2-propanol (SCPi). For example, ECH reacts with chloride, yielding 1,3-dichloro-2-propanol at a rate given by:

$$\frac{dC_{SCPi}}{dt} = (k_{3_i} C_{A_i} + k_{4_i} C_{A_i} C_{H_3O^+})C_{ECH} \qquad \text{Equation 6}$$

The ratio of each substitution product to CPP (initial production, prior to all subsequent product degradation reactions) can be calculated as:

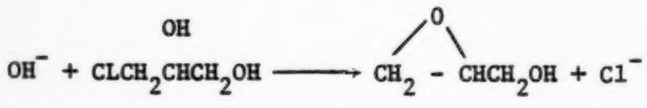
$$\frac{C_{SCP_i}}{C_{CPP}} = \frac{k_{3_i} C_{A_i} + k_{4_i} C_{A_i} C_{H_3O^+}}{k_3 + k_2 C_{H_3O^+}} \qquad \text{Equation 7}$$

The overall degradation rate is the sum of water hydrolysis and all reactions with anions:

$$-\frac{d\,C_{ECH}}{dt} = \frac{d\,C_{CPP}}{dt} + \sum \frac{d\,C_{SCP_i}}{dt} = \left[k_1 + k_2 C_{H_3O^+} + \sum (k_{3_i} + k_{4_i} C_{H_3O^+})C_{A_i}\right] C_{ECH}$$

Equation 8

The initially formed products can react further. The two most common reactions of the initial products are their subsequent hydrolysis to yield 3-chloro-1,2-propanediol or ring closure to yield a new epoxide. An example of the former is the apparent reaction between carbonate or bicarbonate with ECH. Shvets and Aleksanyan (1973) deduced that carbonate (and bicarbonate) directly reacts with ECH from observed reaction kinetics, but a carbonate (or bicarbonate) ester could not be isolated. They concluded that the carbonate (and bicarbonate) esters are hydrolyzed. The epoxide formation is a general base assisted reaction; 3-chloro-1,2-propanediol reacts with hydroxide to yield glycidol (Shell, 1969):



$$OH^- + ClCH_2\overset{OH}{C}HCH_2OH \longrightarrow CH_2 - CHCH_2OH + Cl^-$$

Epoxide formation is discussed further in Section III-A-1-2 (Chemical Degradation in the Environment).

Most of the information necessary for the product and half-life calculations for environmental hydrolysis of ECH either has been experimentally measured or a reasonable value can be estimated from available data. Table 3 summarizes the ECH hydrolysis rate constants, k_1 and k_2. Table 4 lists the experimentally derived rate constants, k_2 and k_4, for anion reactions with ECH.

Rate constants can be calculated at any temperature with the activation energy, E_A, by the Arrenhius equation:

$$\ln\left(k_1/k_2\right) = \frac{E_A}{R}\left(\frac{1}{T_2} - \frac{1}{T_1}\right) \qquad \text{Equation 9}$$

where R is the gas constant and T is the absolute temperature. Activation energies only were available for a few of the ECH hydrolysis reactions (Table 5),

Table 3. Rate Constants for Hydrolysis of Epichlorohydrin

Temperature (°C)	$10^6 k_1$ (s^{-1})	$10^5 k_2$ ($1\ mol^{-1} s^{-1}$)
0.0		6.91[a]
20.0	0.97[b]	43.4[a,b]
25.0		68.2[c], 77[a]
35	5.9[d]	
37	5.3[e]	
45	13.8[d]	
50	20.4[d]	
75	129[d]	
85	246[d]	

[a] Pritchard and Siddiqui, 1973

[b] Brönsted, Kilpatrick, and Kilpatrick, 1929

[c] le Noble and Duffy, 1964

[d] Shvets and Aleksanyan, 1973

[e] Ross, 1962

Table 4. Rate Constants for Epichlorohydrin Reaction with Various Anions

Anion	Temperature, °C	$10^5 k_3$ ($l\ mol^{-1} s^{-1}$)	$10^2 k_4$ ($l^2\ mol^{-2} s^{-1}$)
Chloride, Cl^-	20	1.15[a], 0.99[c]	0.45[a]
	40	6.3[b]	6.8[b]
Bromide, Br^-	20	6.2[a], 6.3[c]	2.2[a]
Iodide, I^-	20	10.0[a]	
Thiosulfate, $S_2O_3^=$	20	6.3[a]	
Formate, HCO_2^-	20	0.47[a]	
Benzoate, $C_6H_5CO_2^-$	20	0.52[a]	
Acetate, $CH_3CO_2^-$	20	0.62[a]	
	37	3.33[c]	
Nitrate, NO_3^-	20	0.022[d]	
Bicarbonate, HCO_3^-	65	0.17[e]	
	75	0.30[e]	
	80	0.52[e]	
	85	0.68[e]	
Carbonate, $CO_3^=$	35	0.42[e]	
	45	0.83[e]	
	50	1.42[e]	
	60	2.5[e]	

---

[a] Brönsted, Kilpatrick, and Kilpatrick, 1929

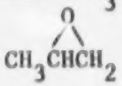
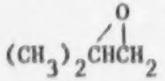
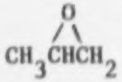
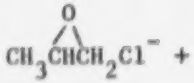
[b] Addy and Parker, 1965

[c] Ross, 1950

[d] Petty and Nichols, 1954

[e] Shvets and Aleksenyan, 1973

Table 5. Activation Parameters for Epichlorohydrin Hydrolysis Reactions

Reference	Reaction	E_A	$\Delta S^{\ddagger}$
Shvets and Aleksanyan, 1973	$ECH + HCO_3^- \longrightarrow$	18.4 ± 0.8	-21.7 ± 0.9
	$ECH + CO_3^{=} \longrightarrow$	17.7 ± 0.7	-16.8 ± 0.7
Pritchard and Siddiqui, 1973	$ECH + H_3O^+ \longrightarrow$	19.86 ± 0.91	-8.1 ± 3.2
	 $CH_3\overset{O}{\widehat{CHCH}}_2 + H_3O^+ \longrightarrow$	19.01 ± 0.23	-5.1 ± 0.8
	 $(CH_3)_2\overset{O}{\widehat{CHCH}}_2 + H_3O^+ \longrightarrow$	19.34 ± 0.23	+7.9 ± 0.8
Addy and Parker, 1965	 $CH_3\overset{O}{\widehat{CHCH}}_2 + Cl^- \longrightarrow$	18.8 ± 0.9	-22.2 ± 2.7
	 $CH_3\overset{O}{\widehat{CHCH}}_2Cl^- + H_3O^+ \longrightarrow$	18.3 ± 0.9	-3.4 ± 2.7

but this limited group includes the most significant environmental reactions: hydrolysis and the reactions with chloride, carbonate, and bicarbonate. The activation energies are in the narrow range of approximately 17.5 to 20 kcal/mole. An E_A of ca. 19 kcal/mole is suggested as an estimate for other anion reactions.

Brönsted and coworkers (1929) noted a proportionality between the rate constants for catalyzed and uncatalyzed reactions:

$$\frac{k_2}{k_1} = \frac{k_4}{k_3} \approx 450$$

Their data was limited to the hydrolysis (reaction with water) and the reactions with chloride and bromide at 20°. Petty and Nichols (1954) reported k_3 and k_4 with approximately this ratio for ECH reaction with nitrate at 20°, also. If this ratio does extend to all anions, then for prevalent environmental conditions the acid catalyzed reactions will not significantly contribute to the hydrolysis rates. For this approximate ratio, Equation 6 yields the following rates for pH 7 and pH 4, respectively (see below):

$$\frac{d\, C_{SCP}}{dt} = \left(k_3\, C_A + 450 \times 10^{-7}\, k_3\, C_A\right) C_{ECP} \approx k_3\, C_A\, C_{ECP}$$

$$\frac{d\, C_{SCP}}{dt} = \left(k_3\, C_A + 450 \times 10^{-4}\, k_3\, C_A\right) C_{ECP} \approx 1.05\, k_3\, C_A\, C_{ECP}$$

The Swain-Scott relationship provides an excellent estimate for k_3 values (Ross, 1964; Petty and Nichols, 1954):

$$\log ka/ko = sn$$

where ka and ko (= $k_1/55.56$) are rate constants for anion reaction and hydrolysis, respectively, and s and n are the substrate (0.93 for ECH) and nucleophile constants, respectively. It could be used to estimate the rate for anions for which no experimental values are listed. Table 6 summarizes values for n.

Although very little information was available for EBH, a study by Pritchard and Long (1956) on hydrolysis rates at 0° for both ECH and EBH, as well as other epoxides, demonstrated that the two epihalohydrins have almost identical rates and undoubtedly have similar mechanisms. The rate constants (as log k_1) were linear as functions of H_o, but not when graphed as functions of C_{H^+}. At $H_o = 0$, the rate constants for ECH and ECB, respectively, were $3.8 \times 10^{-5}\ s^{-1}$ and $4.8 \times 10^{-5}\ s^{-1}$ and had slopes (log k_1 vs. $-H_o$) of 0.86 and 0.87, respectively.

Equation 7 was used to calculate ECH half-lives for hydrolysis in distilled water (pH 7) and sea-water (pH 7, 3% NaCl) at 20°. Hydrolysis rate constants applied to the calculations are $k_1 = 1 \times 10^{-6}\ s^{-1}$; $k_2 = 4.3 \times 10^{-4}\ l\ mol^{-1}\ s^{-1}$; $k_3 = 1 \times 10^{-5}\ l\ mol^{-1}\ s^{-1}$; and $k_4 = 0.5 \times 10^{-2}\ l^2\ mol^{-2}\ s^{-1}$. Degradation half-times were 8.0 days in distilled water and 5.3 days in 3% NaCl. The product ratio of 1,3-dichloro-2-propanol:3-chloro-1,2-propanediol was calculated by Equation 8 as 2:1.

In conclusion, ECH and ECB will hydrolyze in the environment. The half-life and products will vary with the ionic content of the water. The maximum half-life for ECH at 20° is about 8 days. ECH is expected to hydrolyze faster if the water contains high chloride or high carbonate-bicarbonate content. While the hydrolysis product is 3-chloro-1,2-propanediol, significant concentrations of other products can be formed from reaction with aqueous anions. These products include 1,3-dichloro-2-propanol from reaction with aqueous chloride. The initial products can react further (see Section III-A-1-b).

Table 6. Values for Calculating Epichlorohydrin Reaction Rates with Various Nucleophiles Using the Scott-Swain Relationship[a] (adapted from Ross, 1962)

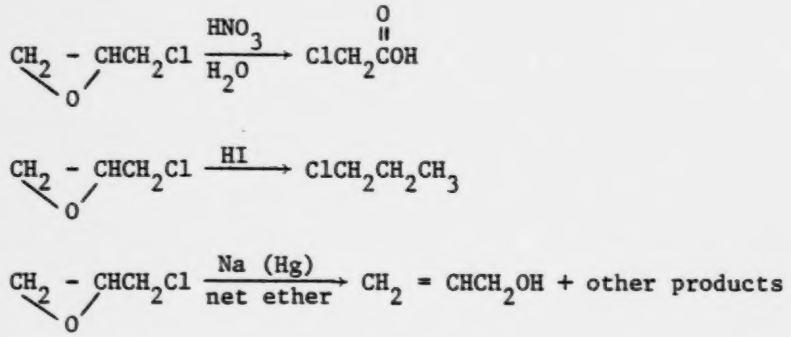
Nucleophile	n
H_2O	0
$SO_4^{=}$	2.5
$CH_3CO_2^-$	2.72
Cl^-	3.04
C_6H_5N	3.6
OH^-	4.2
SCN^-	4.77
I^-	5.04
MS^-	5.1
$S_2O_3^{=}$	6.36

[a] log ka/ko = 0.93n

EBH will react in analogous pathways and, most probably, at a slightly faster rate.

2. Oxidation

Shell Chemical Company (1969) lists several oxidation and reduction reactions of ECH:



None of these reactions are important in the environment.

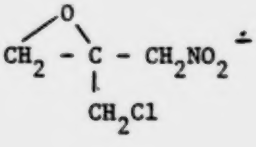
The epihalohydrins can be oxidized by free radical processes in liquid phase (Dobbs *et al.*, 1976; Beckwith, 1972) or gas phase (Dilling *et al.*, 1976). These reactions probably occur in epihalohydrin oxidation in photochemically initiated atmospheric reactions (Gay and Bufalini, 1971; Bufalini, 1971). The liquid phase free-radical oxidations which are discussed herein are probably not important in environmental waters, but they are possible mechanisms by which the epihalohydrins are oxidized with atmospheric free-radical initiators.

Available literature only evaluated the mechanisms of liquid phase reactions with a few free radical initiators. The epihalohydrins yield free-radicals which, in part, depend upon the radical initiator. Dobbs and coworkers (1976) suggested that *t*-butoxyl radical, $(CH_3)_3CO\cdot$, preferentially abstracts an alicyclic hydrogen atom, while hydroxyl radical, HO·, preferentially reacts with acyclic alkyl groups. Their experimental work on the epihalohydrins was limited to the identification of species formed by reactions with hydroxyl radicals produced by the titanium (III) ion-hydrogen peroxide system. ECH yielded two radicals which they identified by electron spin resonance (esr) as:

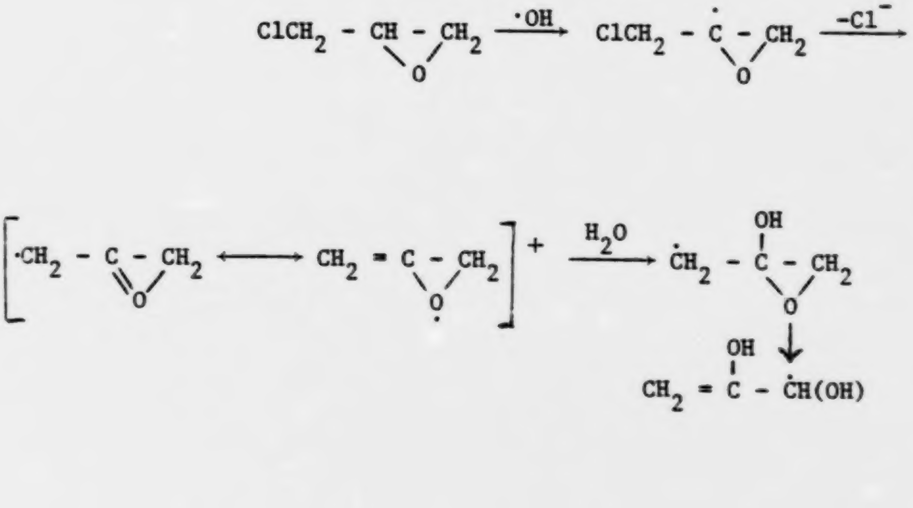
$$CH_2 \overset{\cdots}{-\!-} C(OH) \overset{\cdots}{-\!-} C(OH)CH_3$$

$$\text{and } CHCl \overset{\cdots}{-\!-} CH \overset{\cdots}{-\!-} CH(OH)$$

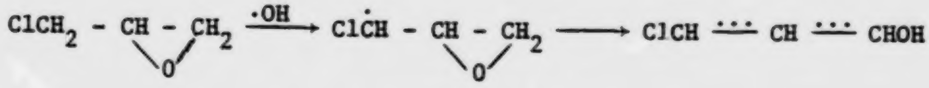
Also, they trapped the initially formed radicals with nitromethane and identified the only new adduct by means of esr as:



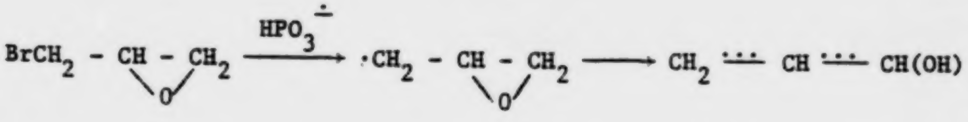
They interpreted the results as evidence for two pathways of hydrogen abstraction. Dobbs and coworkers suggested that the propenediol radical formed by the sequence:



The tertiary radical initially generated would also yield the nitromethylene adduct observed by esr. A second radical would explain the chloropropenol radical:



Another type of radical abstraction reaction has been identified with EBH (Dobbs et al., 1976; Beckwith, 1972). The system of titanium (III) - hydrogen peroxide - phosphorous acid or hypophosphorous acid will yield various phosphorus-containing radicals: $\cdot HPO_2^-$; $\cdot HPO_3^-$; $\cdot PO_3^{2-}$; etc. These phosphorous radicals will abstract bromine atoms, rather than hydrogen atoms, from organics activated by resonance. However, the phosphorous radicals will not abstract chlorine atoms from analogous structures (Beckwith, 1972). EBH will react to yield an allylic alcohol radical:



Dilling and coworkers (1976) evaluated ECH photolysis under simulated atmospheric conditions. They determined the decomposition rate of 10 ppm ECH in an atmosphere containing 5 ppm nitric oxide. They did not report products. They photolyzed with two 275 W reflector sunlamps (cutoff at 290 nm) which emitted UV light with intensity ∿2.6 times the natural sunlight at noon in summer in Freeport, Texas. The ECH half-life was 16.0 hours. These conditions are expected to generate the free-radical processes of the photochemical smog cycle (Levy, 1973). Since they did not report any direct photolysis (see below), no information is available to speculate on degradation by processes other than gas phase radical reactions initiated by species expected in the photochemical smog cycle.

3. Photolysis

No ultraviolet absorption data were available for the epihalohydrins. Neither the alkyl halides nor epoxides have strong absorption in the sunlight region (wavelengths above 300 nm) (Calvert and Pitts, 1966). The epihalohydrin absorption maxima are probably below 250 nm and, at most, will have the tail ends of their absorption peak above 300 nm. No significant environmental photochemistry is expected.

II. Environmental Exposure Factors

A. Production and Consumption

1. Quantity Produced

The total U.S. production of ECH for 1973 was estimated to be approximately 345 million lbs. (Oosterhof, 1975). This included roughly 160 million lbs. of ECH as a feedstock for the manufacture of glycerin and 180 million lbs. of refined ECH, most of which went into production of epoxy resins. Current production of ECH is judged to be higher than the 1973 estimate. Industry expanded production capacity from 450 million lbs. in 1975 to 640 million lbs. annually by the end of 1978 (SRI, 1977). Market trends discussed in Section II-A-5 can be used to estimate the 1977 production level of ECH as roughly 400 million lbs. Table 7 lists data for the production and sales of refined ECH from 1958 through 1973, with an estimated breakdown of sales for 1973. Note from Table 7 that the quantity sold represents but a fraction of the manufactured totals, much of which was (and still is) used captively for producing glycerin, epoxy resins, and other products (Table 8).

The sole U.S. manufacturer of EBH, Great Lakes Chemical Corporation (1978), has indicated that as of January, 1978, they last produced a batch of EBH in 1975. The batch amounted to roughly 20,000 lbs. While they have retained the ability to manufacture more in the future, they will do so only on the demand of a customer, as the chemical is no longer an intermediate for any other Great Lakes product. It therefore appears that EBH is only marginally a commercial product, marketed by small companies such as Aldrich Chemical, for sale as a research material.

Table 7. U.S. Production and Sales of Refined Epichlorohydrin (Millions of pounds) (Oosterhof, 1975)

Year	Production[a]	Sales[b]
1958	---	12.7
1959	---	25.2
1960	---	29.3
1961	---	20.1
1962	68.8	19.3
1963	---	---
1964	(85)[d]	32.0
1965	---	---
1966	---	---
1967	---	---
1968	---	75.0
1969	(130)	---
1970	---	---
1971	---	---
1972	---	---
1973	(180)	(95)[c]

[a] Data include production for captive use in the manufacture of epoxy resins and other products. Data exclude production of crude epichlorohydrin used in the manufacture of synthetic glycerin.

[b] Data include exports.

[c] Sales of refined epichlorohydrin in 1973 by the two U.S. producers have been estimated to be as follows (Oosterhof, 1975):

Estimated Sales--1973	Millions of Pounds
For epoxy resins (estimated at about 35% of the total consumption for epoxy resins of 130 million pounds)	45
For epichlorohydrin elastomers	6
For other products	31
For export	13
Estimated total sales	95

[d] Figures in parenthesis are estimated.

Table 8. Estimated U.S. Consumption and Exports of Epichlorohydrin - 1973 (Millions of Pounds) (Oosterhof, 1975)

	Crude Epichlorohydrin	Refined Epichlorohydrin
Synthetic Glycerin	160[a,b]	--[a]
Epoxy Resins	134	130
Epichlorohydrin Elastomers	6	6
Other Products	32	31
Exports	13	13
Total Consumption	345	180

[a] Crude epichlorohydrin used in the manufacture of synthetic glycerin is not included in the production and sales data for refined epichlorohydrin published by the U.S. International Trade Commission.

[b] Chemical Marketing Reporter (1978) indicates that the demand for epichlorohydrin in the synthetic glycerin market has shrunk from 134 million pounds in 1973 to about 65 million in 1977.

2. Producers, Distributors, Production Sites, and Capacities

ECH is produced by Shell Chemical Company and Dow Chemical USA. Plant sites and capacities are listed in Table 9. In addition, Ciba-Geigy Corporation (Toms River, New Jersey) and Union Carbide Corporation (Institute, West Virginia) have capacities for 35 million lbs. and 25 million lbs., respectively, of refined ECH, although neither have recently produced it.

EBH is listed by Great Lakes Chemical Corporation as a current product, but according to a spokesman for the company they ceased using it captively six or seven years ago when a flame retardant for which it was an intermediate was dropped from their product line. They do, however, retain the capacity to produce EBH as customers require it. The last batch of about 20,000 lbs. was manufactured at El Dorado, Arkansas, in 1975. The actual capacity of the El Dorado plant to manufacture this chemical is not available.

A number of relatively small chemical companies specializing in rare and research grade chemicals offer ECH and EBH in their catalogs. Two examples are Pfaltz and Bauer of Stamford, Connecticut, and Aldrich Chemical of Milwaukee, Wisconsin. It is likely they purchase refined ECH from one of the two manufacturers mentioned above, and they further purify it, if necessary, before selling it. In the case of EBH, they may find it just as economical to synthesize their own in small batches as to purchase it from Great Lakes.

There is no indication that EBH is imported, but more than 500,000 lbs. of ECH were imported in 1974 (Oosterhof, 1975). This is less

Table 9. Plant Capacity and Site for Epichlorohydrin Manufacture (SRI, 1979)

			Annual Capacity (millions of pounds)
Dow Chemical USA	Freeport, Texas		260*
Shell Chemical Co.	Deer Park, Texas		110
	Norco, Louisiana		110
		Total	480

* To be expanded to 440 million lb/yr.; completing date third quarter 1980.

than 0.5% of the domestic production. Table 10 lists the countries of origin and the quantities involved for that year. An estimated 13 million lbs. were exported in 1973 (Tables 7 and 8).

3. Production Methods and Processes

The "allyl chloride" route is the only economically competitive method for the synthesis of ECH and it is therefore the only one used by Dow and Shell in the United States (Oosterhof, 1975). The raw materials required are propene, chlorine, hypochlorous acid, and an alkali, either sodium or calcium hydroxide. Figure 1 depicts the overall manufacturing sequence.

The first step in the process is the reaction of propene with chlorine under free-radical conditions which favor substitution of a methyl hydrogen with a chlorine atom rather than addition of chlorine to the double bond. Such conditions include the presence of ultraviolet light and/or a catalyst appropriate to encourage chlorine radical formation which initiates a chain reaction:

$$Cl_2 \xrightarrow{h\nu} 2Cl\cdot$$

$$\cdot Cl + H_2C = CHCH_3 \longrightarrow H_2C = C\dot{H}CH_2 + HCl$$

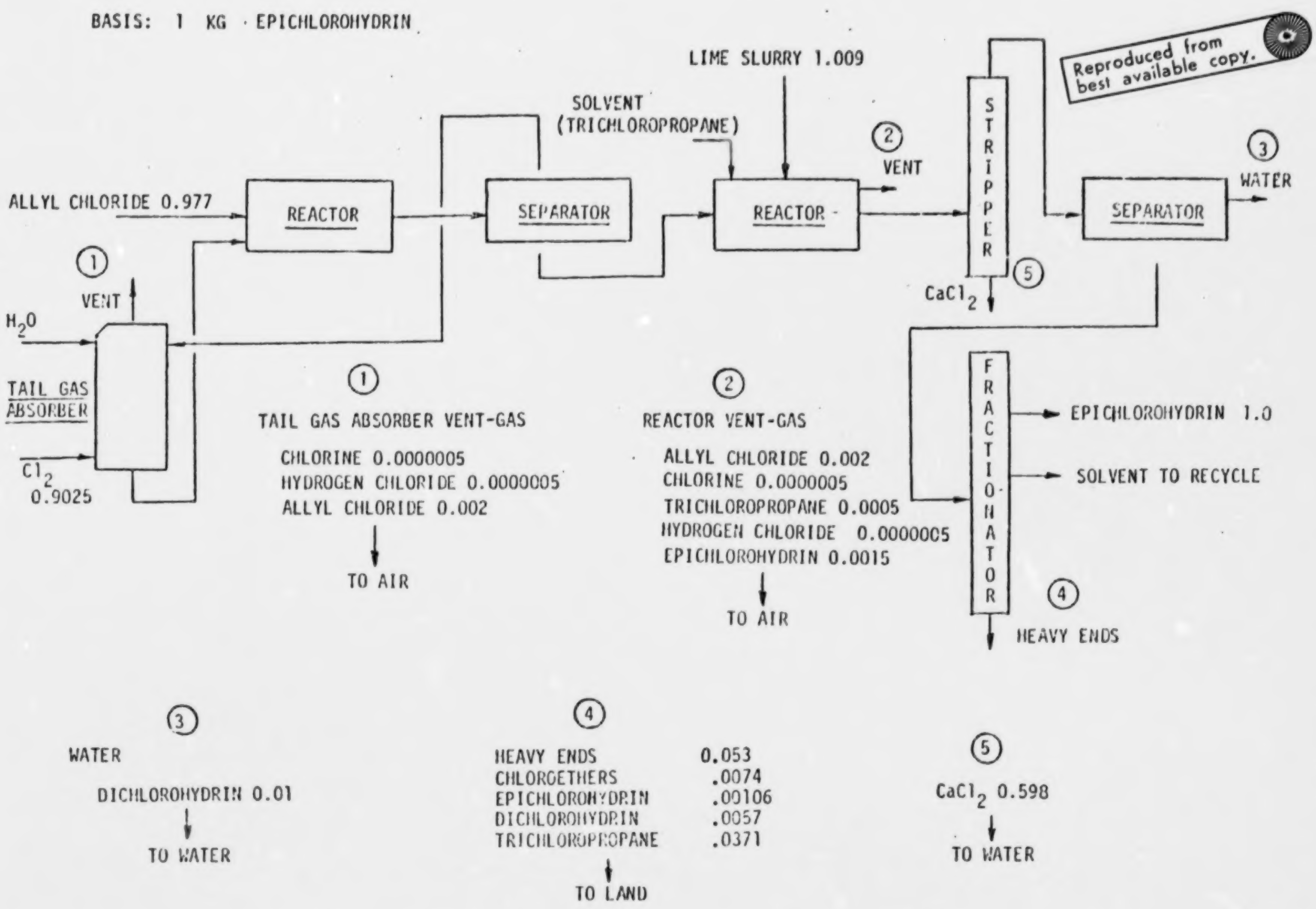
$$H_2C = C\dot{H}CH_2 + Cl_2 \longrightarrow H_2C = CHCH_2Cl + Cl\cdot$$

No matter how the reaction conditions may be adjusted to maximize the production of the desired 3-chloropropene product as shown above, a mixture of by-products is also produced consisting principally of 1,2-dichloropropane and cis- and trans-1,3-dichloropropene. These by-products are isolated and sold in nematocide products (see Section I-A-4).

Table 10. U.S. Imports of Epichlorohydrin, 1974 (Oosterhof, 1975)

Country of Origin[a]	Pounds
Japan	246,917
The Netherlands	165,403
Italy	66,264
United Kingdom	39,154
Canda	15,800
Germany, Federal Republic of	3,596
Total	537,134

[a] Some of the countries mentioned in the table do not produce epichlorohydrin.



BASIS: 1 KG · EPICHLOROHYDRIN
ALLYL CHLORIDE 0.977
REACTOR
SEPARATOR
SOLVENT (TRICHLOROPROPANE)
LIME SLURRY 1.009
REACTOR
② VENT
STRIPPER
⑤
$CaCl_2$
SEPARATOR
③ WATER
①
VENT
H_2O
TAIL GAS ABSORBER
Cl_2 0.9025
FRACTIONATOR
EPICHLOROHYDRIN 1.0
SOLVENT TO RECYCLE
④
HEAVY ENDS
①
TAIL GAS ABSORBER VENT-GAS
CHLORINE 0.0000005
HYDROGEN CHLORIDE 0.0000005
ALLYL CHLORIDE 0.002
TO AIR
②
REACTOR VENT-GAS
ALLYL CHLORIDE 0.002
CHLORINE 0.0000005
TRICHLOROPROPANE 0.0005
HYDROGEN CHLORIDE 0.0000005
EPICHLOROHYDRIN 0.0015
TO AIR
③
WATER
DICHLOROHYDRIN 0.01
TO WATER
④
HEAVY ENDS 0.053
CHLOROETHERS .0074
EPICHLOROHYDRIN .00106
DICHLOROHYDRIN .0057
TRICHLOROPROPANE .0371
TO LAND
⑤
$CaCl_2$ 0.598
TO WATER

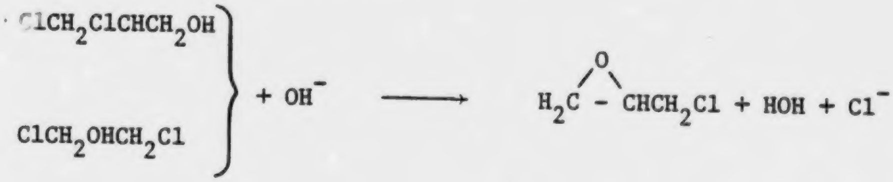
Reproduced from best available copy.

Figure 1. Epichlorohydrin Manufacture (Gruber, 1976)

The second step in the commercial production of ECH is the reaction of the 3-chloropropene (allyl chloride) with hypochlorous acid to yield a mixture of dichlorohydrins (2,3-dichloro-1-propanol and 1,3-dichloro-2-propanol):

$$H_2C = CHCH_2Cl + HOCl \longrightarrow ClCH_2CHClCH_2OH + ClCH_2CHOHCH_2Cl$$

In the third step, the dichlorohydrins are reacted with hydroxide ion (from sodium or calcium hydroxide) to form the epoxide ring:



The resulting crude product is satisfactory for use in glycerin manufacture. It is refined by distillation when destined for use in the manufacture of epoxy resins and other applications requiring pure ECH.

Figure 1 illustrates the process flow for the production of ECH from allyl chloride; the diagram also indicates process by-products and releases. Allyl chloride is fed continuously to a stirred tank where it reacts at atmospheric pressure at 30-40°C in the liquid phase with a solution of hypochlorous acid. The hypochlorous acid is produced in a packed tower by dissolving chlorine in water. The reaction tank effluent is fed to a separator; the upper layer (aqueous phase) is recycled to the hypochlorous acid tower. The underflow, chiefly dichlorohydrins, is fed to the second agitated reactor, where virtually quantitative conversion to epichlorohydrin by reaction with lime slurry takes place. Trichloropropane is used as a solvent for the ECH. The effluent from the second reactor is steam stripped, removing ECH as the water azeotrope. The undercut (calcium chloride solution, and the excess lime, in suspension) is sent to by-product recovery, or discharged through an industrial outfall. The distillate's water and organic phases are separated, with the undercut fed to a fractionating tower for recovery of ECH and solvent. The purified ECH cut is sent to storage. The recovered solvent is recycled (Gruber, 1976).

Dow (1979) and Shell (1979) Chemical Companies have made the following comments regarding Figure 1:

Vent No. 1: Does not exist in shell facilities.

Undergoes further processing at Dow - after processing, atmospheric emissions are essentially negligible with respect to chlorinated hydrocarbons.

Vent No. 2: Shell data show an emissions rate of 0.000005 pound ECH emitted per pound produced.

Dow - same as Vent No. 1.

Stream No. 3: Is recovered by both Dow and Shell processes.

Stream No. 4: Recovered at Shell facilities, no discharge.

Undergoes further chemical processing for recovery or thermal degradation of waste products (none subjected to land disposal).

Stream No. 5: Subjected to biooxidation post treatment at Dow.

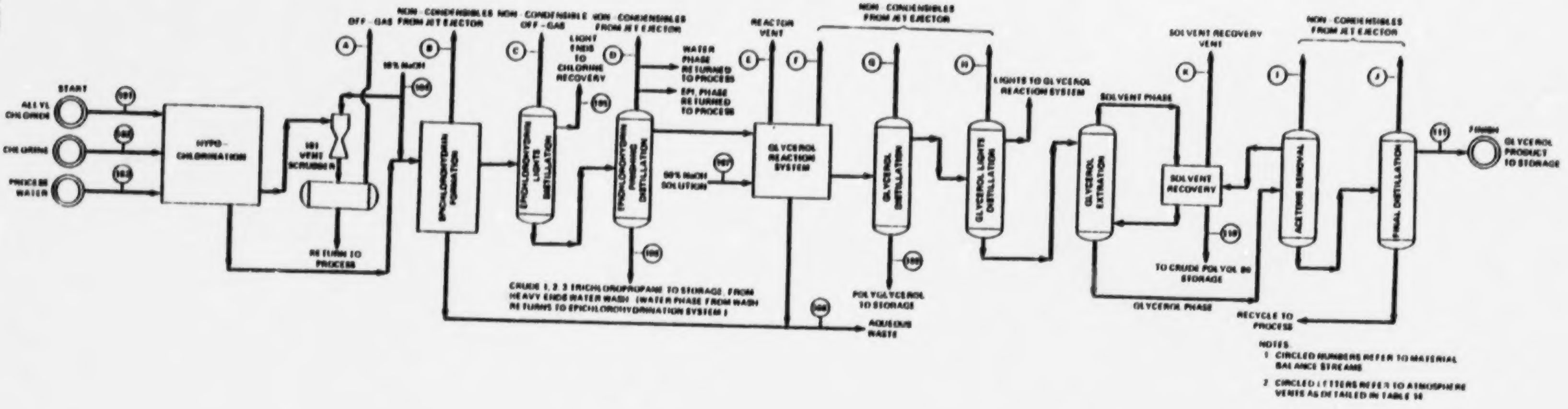
Notes:

(1) The Shell facility has an additional vent not shown on Figure 1; it is atop ECH finishing column and emits 0.0004 pound ECH per pound production.

(2) Shell estimates ECH waste from Shell facility to amount to 0.00045 pound total per pound production.

(3) Dow estimates emission from process vents and storage tanks to be less than 0.00003/lb.

A large fraction of ECH production is used to make glycerin. In this process, the ECH is not purified or isolated from the system, but rather, is used in a continuous flow operation. This entire operation is shown in Figure 2.


START
ALLYL CHLORIDE
CHLORINE
PROCESS WATER
101
103
HYPO-CHLORINATION
101 VENT SCRUBBER
RETURN TO PROCESS
OFF - GAS
A
10% NaOH
104
NON - CONDENSIBLES FROM JET EJECTOR
B
EPICHLOROHYDRIN FORMATION
NON - CONDENSIBLE OFF - GAS
C
LIGHT ENDS TO CHLORINE RECOVERY
105
EPICHLOROHYDRIN LIGHTS DISTILLATION
NON - CONDENSIBLES FROM JET EJECTOR
D
WATER PHASE RETURNED TO PROCESS
EPI, PHASE RETURNED TO PROCESS
EPICHLOROHYDRIN FINISHING DISTILLATION
106
CRUDE 1, 2, 3 TRICHLOROPROPANE TO STORAGE, FROM HEAVY ENDS WATER WASH (WATER PHASE FROM WASH RETURNS TO EPICHLOROHYDRINATION SYSTEM)
50% NaOH SOLUTION
107
REACTOR VENT
E
F
GLYCEROL REACTION SYSTEM
108
AQUEOUS WASTE
NON - CONDENSIBLES FROM JET EJECTOR
G
GLYCEROL DISTILLATION
109
POLYGLYCEROL TO STORAGE
H
GLYCEROL LIGHTS DISTILLATION
LIGHTS TO GLYCEROL REACTION SYSTEM
GLYCEROL EXTRACTION
SOLVENT PHASE
GLYCEROL PHASE
SOLVENT RECOVERY VENT
K
SOLVENT RECOVERY
110
TO CRUDE POLYOL 80 STORAGE
NON - CONDENSIBLES FROM JET EJECTOR
I
ACETONE REMOVAL
J
FINAL DISTILLATION
RECYCLE TO PROCESS
111
FINISH
GLYCEROL PRODUCT TO STORAGE

NOTES:
1 CIRCLED NUMBERS REFER TO MATERIAL BALANCE STREAMS
2 CIRCLED LETTERS REFER TO ATMOSPHERE VENTS AS DETAILED IN TABLE 14

Figure 2. Glycerin (Glycerol) Manufacture (Pervier et al., 1974)

EBH could be made by a similar route, although the tendency to form products other than 3-bromopropene in the first step would be rather high. This would tend to raise the cost of EBH even if it were made on as large a scale as ECH. Blicke and Anderson (1954) report that EBH can be prepared in 85-90% yields from γ,β-dibromohydrin, which is made from $CH_2{:}CHCH_2OH$ and Br_2.

Many chemical plants are capable of producing ECH from purchased 3-chloropropene by running the last two steps of the sequence shown above. Ciba-Geigy and Union Carbide used to make ECH this way (Oosterhof, 1975). However, the economics of this route have been very unfavorable in recent years and will probably remain so in the foreseeable future.

4. Market Prices

Prices for commercial quantities of EBH are not available since this product is not presently marketed. In research quantities, it is available from Aldrich Chemical Company for $5 per 100 grams, or $15 per 500 grams (Aldrich, 1977). Other specialty chemical vendors are selling it for about the same price.

The price of ECH in 1954 was 37¢/lb. (tank cars, f.o.b. works). It declined over the next decade to 27¢/lb. (tank cars, delivered) in 1964. Then, after a decade of stability, the price rose to 35-38¢/lb. in 1975 (Oosterhof, 1975) and is currently about 48¢/lb. (tank cars, delivered) (Chemical Marketing Reporter, 1978a).

5. Market Trends

According to Oosterhof (1975), the total amount of ECH used for the manufacture of glycerin will remain constant over the next few years, even though the total quantity of glycerin produced will increase at a rate of about 2-3% per year; the balance will be manufactured by other means. Demand for ECH for other purposes is expected to grow at about 6-7% annually due to a 10% growth rate anticipated for its main use, epoxy resins. The total U.S. capacity for ECH production is expanding to meet this increased demand and is estimated to reach approximately 640 million pounds by the end of 1978 (see Section II-A-2).

The Chemical Marketing Reporter (1978b) has indicated that Shell expects a growth rate of 0 to 1% for ECH over the next 5 years; in contrast Dow indicated that the glycerin decline has been offset by a 8% increase in the epoxy resin market resulting in a 3% per year increase since 1976.

B. Use of Epihalohydrins

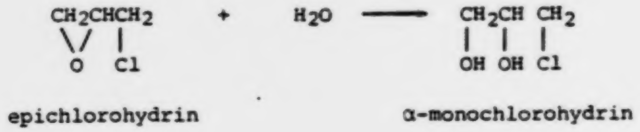
1. Major Uses and Their Chemistry

ECH is primarily consumed as a chemical intermediate in the production of epoxy resins and glycerin. The uses of ECH in 1973 are outlined in Table 7 (see Section II-A-1). On a percentage basis, they were as follows: glycerin, 46%; epoxy resins, 39%; exports, 4%; elastomers, 2%; and other products, 9%. Current uses are judged to be generally the same, with a slight rise in percentage going for epoxy resin production.

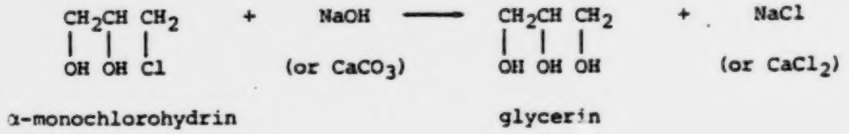
The only current use of EBH at the present time appears to be as a laboratory research reagent. The remainder of this section is therefore devoted exclusively to the major uses of ECH. Minor uses of ECH are described in Section II-B-2.

a. Synthetic Glycerin

Approximately 37% of the total industry capacity to produce glycerin (both synthetic and natural) is based upon synthesis from ECH (Oosterhof, 1976); about 65.5% of the synthetic capacity is based upon synthesis from ECH. The chemical reaction for this synthesis can be represented as follows (Oosterhof, 1976):



$$\underset{\text{O}\qquad\text{Cl}}{CH_2CHCH_2} + H_2O \longrightarrow \underset{\text{OH OH Cl}}{CH_2CH\;CH_2}$$



$$\underset{\text{OH OH Cl}}{CH_2CH\;CH_2} + \underset{(\text{or } CaCO_3)}{NaOH} \longrightarrow \underset{\text{OH OH OH}}{CH_2CH\;CH_2} + \underset{(\text{or } CaCl_2)}{NaCl}$$

The manufacturers who produce glycerin from ECH (Dow Chemical in Freeport, Texas, and Shell Chemical in Deer Park, Texas) produce it in a continuous operation, as depicted in Figure 2 (Section III-A-3). In actuality, the ECH in this process is only an intermediate which is not isolated from the system. ECH is fed into aqueous caustic in a stirred reaction maintained at 150°C. Reaction time is 30 minutes. A solution of 5% glycerin content is produced along with salts (sodium or calcium chloride). The crude glycerin is concentrated to 80% with multiple-effect evaporators. Salt is removed by centrifuge and the glycerin is again concentrated and desalted to yield 98% glycerol. After colored impurities are removed by solvent extraction, the glycerol is purified by steam distillation (Lowenhein and Moran, 1975; Kern, 1966).

Glycerin is used in drug and chemical manufacture, food products, tobacco products, and cellophane, as well as other uses. No information described the specific uses of glycerin produced from ECH. Also, no information was available describing residual ECH in the glycerin. Based upon the expected hydrolysis behavior (see Section I-B-1) and manufacturing processes, no significant ECH should remain in the final product.

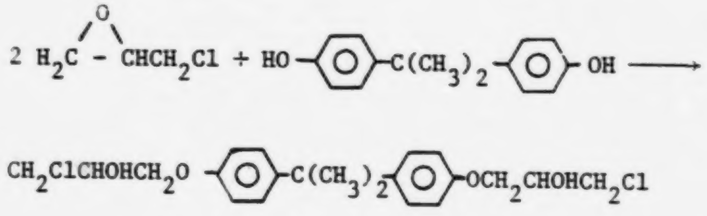
b. Epoxy Resins

Epoxy resins are commercially used in protective coatings, bondings and adhesives, and reinforced plastics. According to Weschler (1965), consumption for 1963 had the following pattern:

bonding and adhesives	16%
protective coatings	43%
reinforced plastics	14%
other uses	27%

The term "epoxy resin" is assigned to polymeric materials containing epoxide groups. Weschler has noted the epoxy resins are actually intermediates; a curing or hardening agent is required to convert the epoxide resin to a thermoset material. The thermoset materials are noted for toughness, adhesion, chemical and abrasion resistance, and electrical insulation. Although the epoxies are more expensive than any other thermosetting plastics, their high consumption results from their unique combination of the above properties.

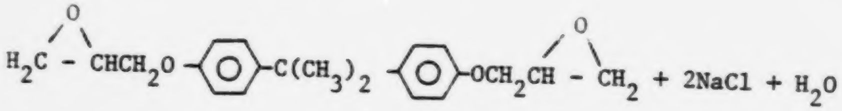
Almost all (90% - Chemical Marketing Reporter, 1978b) commercially produced epoxy resins are made by the reaction between ECH and 2,2-di(4-hydroxyphenyl)propane (also known as 4,4'-isopropylidenediphenol or bisphenol A) (EPA, 1974). The two reagents are dissolved in methanol and placed in a reactor. Sodium hydroxide is added and the mixture refluxed at 171°F (Monsanto Research Corp., 1976). The following reaction sequence takes place (EPA, 1974). First, the ECH and 2,2-di(4-hydroxyphenyl)-propane react to form a chlorohydrin (I):



I

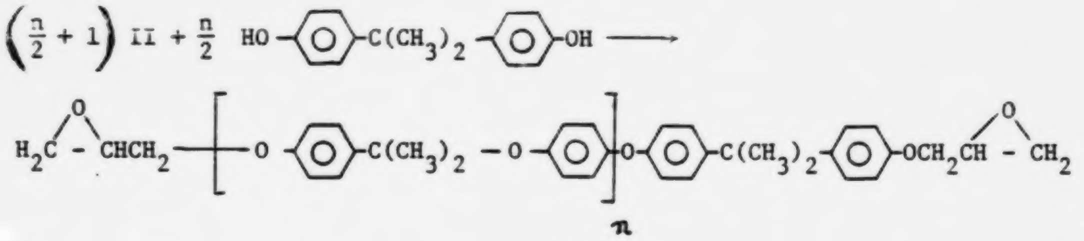
Alkali converts the chlorohydrin intermediate to an ether with terminal epoxy groups (II):

I + NaOH ⟶



II

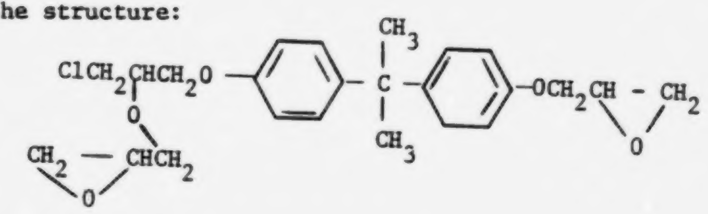
II can now react with additional 2,2-di(4-hydroxyphenyl)propane by the same sequence to yield a long chain compound with terminal epoxy rings (III):



III

Any excess ECH in the product is removed by vacuum (Monsanto Research Corp., 1976).

The chain length, n, of III determines the properties of the product. Chain length is controlled by reactant concentrations, catalysts, and other reaction parameters. The epoxy resins are mixtures of various molecular weight polymers. Low molecular weight liquid products have a relatively low concentration of III and a high concentration of II (i.e., $n < 1$ and ranges between 0.1 to 0.6). High molecular weight solid epoxies have n in the range 1.8 to 16 (EPA, 1974). Also, polymers containing undesirable branched chains form; these have the structure:



Formation of branched chain products are minimized by reactant concentrations, catalysis, other reaction parameters, and equipment design.

When the hardening agent is added to the epoxy, very extensive cross-linking occurs, resulting in the desired final properties of the cured material. Curing agents are selected from a variety of chemicals capable of reacting with either the epoxy or hydroxy groups in the resin. An agent is selected on the basis of the final properties desired. Suitable hardeners include Lewis acids, polyamides, amines, acids, acid anhydrides, and urea or melamine formaldehyde resins, as well as other resins (EPA, 1974).

The estimated consumption of refined ECH for unmodified epoxy resins in 1973 is listed in Table 11. Table 12 lists the major producers of unmodified epoxy resins along with product tradenames and capacities. It may be possible that the resin product contains a small amount of unreacted ECH as a contaminant.

2. Minor Uses of Epichlorohydrin

a. Epichlorohydrin Elastomers

Epichlorohydrin elastomers were developed and patented by Hercules, Inc. In 1964, Hercules granted an exclusive license to B.F. Goodrich Chemical Co. to produce and distribute certain types of epichlorohydrin elastomers. Production of Hydrin 100®, a homopolymer of epichlorohydrin, and Hydrin 200®, an equimolar copolymer of epichlorohydrin and ethylene oxide, was started by Goodrich Chemical in 1965 in semicommercial facilities at Avon Lake, Ohio. The production capacity of the Avon Lake plant was expanded to 8 million lbs. per year in 1969 (Oosterhof, 1975).

Hercules started production of Herclor H®, a homopolymer of epichlorohydrin, and Herclor C®, a copolymer of epichlorohydrin and ethylene oxide, at Hattiesburg, Mississippi, in May, 1970. The plant has a capacity of 10 million lbs. per year (Oosterhof, 1975).

Both types of epichlorohydrin rubber have outstanding resistance to ozone, oil, chemicals, and solvents, and have excellent impermeability to gases. The copolymer has higher resilience and better flexibility at low temperatures. Applications include automotive and aircraft parts, seals and gaskets, wire and cable jackets, hose and belting, adhesives, packing applications, and rubber-coated fabrics. It is estimated that the U.S. production of these elastomers amounted to about 7 million lbs. in 1973, and that the

Table 11. Estimated U.S. Consumption of Refined Epichlorohydrin for Unmodified Epoxy Resins, 1973 (Oosterhof, 1975)

	Unmodified Epoxy Resin Production		Epichlorohydrin Consumption	
Type of Epoxy Resin	Percent of Production	Production (millions of pounds)	Pounds per Pound of Resin	Millions of Pounds
Conventional DGEBA Resins[a]	90%	200.5		121.6
Liquid types (65%)	58.5	130.3	0.68	88.6
Solid types (35%)	31.5	70.2	0.47	33.0
Epoxy Novolac Resins	4	8.9	0.73	6.5
Phenoxy Resins	2	4.5	0.40	1.8
Subtotal	96%	213.9	0.61	129.9
Cycloaliphatic and Other Resins	4	8.9	0	0
	100%	222.8	0.59	129.9

---

[a] Diglycidyl ether of bisphenol A resins, based on epichlorohydrin and bisphenol A.

Table 12. Producers and Sites of Unmodified Epoxy Resins (SRI, 1977)

			Annual Capacity (millions of pounds)
Celanese Corp. Celanese Coatings and Specialty Chems. Co., subsid. Celanese Resins Div.	Louisville, Ky.	(Epi-Rez®)	25
Ciba-Geigy Corp. Plastics and Additives Div. Resins Dept.	Toms River, N.J.	(Araldite®)	60
Dow Chem. U.S.A.	Freeport, Tex.	(D.E.R.®)	75
Haven Indust., Inc. Haven Chem. Div.	Philadelphia, Pa.	Epiphen®	<1
Polychrome Corp. Cellomer Corp., subsid.	Newark, N.J.		n.a.
Pratt & Lambert, Inc.	Buffalo, N.Y.		n.a.
Reichhold Chems., Ind.	Andover, Mass. Azusa, Calif. Detroit, Mich. Houston, Tex.	(Epotuf®)	32
Resyn Corp.	Linden, N.J.	(Resypox®)	40
Seton Co. Wilmington Chem. Corp., div.	Wilmington, Del.		4
Shell Chem. Co.	Deer Park, Tex.	(Epon®)	100
Union Carbide Corp. Chems. and Plastics, div.	Taft, La.		6
		Total	<343

consumption of ECH in manufacturing the elastomers was about 6 million lbs. (Oosterhof, 1975). It is again possible that the final elastomer product may contain a small amount of ECH as contaminant.

b. Other Uses

A variety of other products are produced from ECH, most of them in relatively small volumes. Among them are glycidyl ethers, some types of modified epoxy resins, wet-strength resins for the paper industry, water treatment resins, surfactants, and ion-exchange resins. The available breakdown, by use, for the 1973 consumption of ECH in these uses is listed below (Oosterhof, 1975):

Glycidyl ethers and modified epoxy resins	6 million lbs.
Wet-strength resins	6 million lbs.
Water treated resins	5 million lbs.
Surfactants	4 million lbs.
Miscellaneous applications	10 million lbs.
Total	31 million lbs.

Some of the miscellaneous applications of ECH include intermediates for plasticizers, dyestuffs, pharmaceuticals, oil emulsifiers, and lubricants (Lichtenwalter and Riesser, 1964). It is also used as a stabilizer in chlorine containing materials such as chlorinated rubber and chlorinated insecticides (Shell, 1969; Sayed _et al_., 1974). ECH is also registered as an inactive ingredient in numerous pesticide formulations and is added as a stabilizer to dibromochloropropane (DBCP) (Von Sumpter, 1978).

3. Discontinued Uses

EBH was used formerly as an intermediate in the manufacture of a nematocide by Great Lakes Chemical Corporation. The product was discontinued some years ago and EBH has not had commercial significance since.

4. Proposed Uses

ECH has been recommended as a good solvent for cellulose acetate and rosin and ester gums (Shell, 1969), although its toxicity may preclude such use. It has been proposed as a solvent for chlorosilanes for treating cotton fabrics to improve their dimensional stability (Dorset, 1969). It has also been suggested as a soil fumigant for the control of wireworms (Shell, 1969).

ECH has been documented as a suppressor of male fertility for a number of species, including rats, guinea pigs, sheep, pigs, and hamsters. Kalla and Bansal (1977) have suggested that the effect is due to the alkylation of testicular cysteine, removing the protective effect of cysteine in seminal physiology. The authors suggest that administering ECH and copper ions simultaneously might inhibit the cysteine and allow the copper ions to act as an effective spermicide. Although the authors feel that an alkylating agent will not necessarily induce tumors, the safety of ECH as a contraceptive agent would have to be demonstrated before this proposed use could be considered seriously.

Another suggested use for ECH is the treatment of rice in the canning process (Rutledge and Islam, 1973). Rice is seldom found in canned food because the grains do not hold up well under the canning process; clumping, matting, and disintegration of the grains render the product unpalatable. Treating the rice with ECH cross-links the starch granules and produces a stable rice which could retain favorable organoleptic properties after canning. The authors did not discuss the possibility of ECH residues in the canned product.

5. Alternatives to Uses

Glycerin is being manufactured by at least three processes other than ECH hydrolysis. None require chlorinated hydrocarbons as intermediates (Kern, 1966; Oosterhof, 1975). Since they are already competitive economically with ECH, their replacement of it would be a function of production capacity rather than economics or technology. In fact, the ECH share of the total glycerin production has recently diminished (Oosterhof, 1975). The acrolein-allyl alcohol route for manufacturing glycerin utilizes propene, 2-butanol, and hydrogen peroxide as starting materials. Methyl ethyl ketone is the major by-product. The allyl alcohol-peracetic-glycidol route requires propylene oxide and peracetic acid as starting materials. Acetic acid is the major by-product. The saponification and the high temperature hydrolysis of fats and oils produce large quantities of glycerin which are recoverable from the aqueous layer.

The unique properties of epoxy resins and ECH elastomers (see Sections II-B-1 and 2) are difficult to replace, especially if the use of closely related chemicals such as EBH or halogenated 1,2-epoxybutanes were also prohibited. Other compounds containing an epoxy ring could be used to make epoxy resins, but the properties of the resins, as well as manufacturing costs, might be adversely affected by substituting for ECH.

C. Environmental Contamination Potential

1. General

Sources of ECH entry to the environment have been identified. Information has been developed which quantifies discharges from ECH production, from glycerol production, and from industrial waste disposal. A transportation accident was responsible for a massive ECH release. While ECH could be inadvertently produced, the potential hazard from this entry appears negligible.

No information was available to describe EBH entry to the environment. The only potential sources identified were inadvertent production within industrial processes or from environmental transformations of anthropogenic substances. No quantitative data was available concerning EBH formation or if it has ever been found in the environment (see Section II-E).

2. From Production

ECH is manufactured on a large scale. While most of the material is purified and subsequentially used for epoxy resin or elastomer production, a sizeable proportion is converted to glycerin with only partial purification (see Section II-A-1-a). Pollutant generation and discharge to the environment have been evaluated for ECH and for glycerin production (Gruber, 1976; Pervier et al., 1977). Since the information generated on discharges from glycerin production is directly applicable, it will also be discussed in this section rather than with use (see Section III-C-4).

Gruber (1976) has assessed wastes generated during ECH production. The report also presented some information on pollutants emitted to the atmosphere with waste vent gases. The salient details are depicted in Figure 1 (see Section II-A-3); it describes the manufacturing process, atmospheric emissions from various manufacturing stages, and other wastes generated (discussed in Section II-C-5). In addition to ECH, the process discharges chloroethers, dichlorohydrin, trichloropropane, and allyl chloride, which are also hazardous.

Table 13 summarizes the expected annual emissions from ECH manufacture based upon the emissions described in Figure 1 and upon the assumption that roughly 181 thousand metric tons (400 million pounds) of ECH are produced by the same methods industry wide on an annual basis.

Dow (1979) and Shell (1979) have indicated that the Gruber (1976) emission estimates are much too high and do not reflect current technology. Shell (1979) estimates that, on a basis of 400 million pounds per year production, ECH losses would be 18 thousand pounds total which is significantly less than the estimates in Table 13.

Pervier and coworkers (1974) assessed potential discharges to the environment from glycerin manufacture through caustic hydrolysis of ECH. They sent survey letters to ECH manufacturers and received two responses. The manufacturers reported that ECH and other potential hazardous pollutants were formed and were potentially lost to the environment as atmospheric emissions or through liquid or solid wastes. While this section limits discussion to emissions from the manufacturing process, other sections of this report discuss potential losses from storage (see Section II-C-6) and waste disposal (see Section II-C-5) based upon their report.

Environmental losses during the manufacturing process consist of three types of atmospheric emission: continuous air emissions; intermittent air emissions; and fugitive emissions. Fugitive emissions could result from leaks, sampling, gauge glass blowdowns, and equipment purges. Pervier et al. did not specify all sources of intermittent emissions, but did account for two: process start-up and emergency venting.

Vent streams do emit significant concentrations of chlorinated and non-chlorinated hydrocarbons to the atmosphere. Identified constituents of vent gases are:

Table 13. Expected* 1977 Pollutant Generation from Epichlorohydrin Manufacture (Based upon Figure 1) (Gruber, 1976)

	Metric Tons (thousands of pounds)
Reactor Vent Emitted to the Atmosphere	
Epichlorohydrin	273 (600)
Allyl chloride	364 (800)
Trichloropropane	91 (200)
Chlorine	0.1 (0.2)
Hydrogen chloride	0.1 (0.2)
Water from Separator	
Dichlorohydrin	1818 (4000)
Heavy Ends from Fractionator Requiring Disposal	
Epichlorohydrin	193 (424)
Chloroethers	1345 (2960)
Dichlorohydrin	1036 (2280)
Trichloropropane	6745 (14,840)

*Assuming an industry wide annual production of 181 thousand metric tons (400 million pounds)

ECH
1,2,3-trichloropropane
propyl chlorides
dichloropropenes
acrolein
acetone

The two responding manufacturers have supplied descriptive and quantitative data on emissions and emissions controls. Figure 2 (see Section II-A-3) describes the process sequence and specifies vents emitting gases to the atmosphere. Table 14 summarizes salient quantitative and other information for the two plants. One plant has listed ECH emission from only one vent; ECH emission was reported as 0.001539 ton per ton glycerin or 73 tons (66.5 metric tons) annually. The second plant had replied that five vents emitted ECH; total emission was 0.0002036 ton per ton glycerin or 11.2 tons (10.2 metric tons) annually.

The reports by Gruber (1976) and Pervier _et_ _al_. (1974) estimated ECH emissions within an order of magnitude of each other. Approximately 300 tons (273 metric tons) would be a reasonable estimate for total annual ECH emissions from manufacture using these sources. Dow (1979) has indicated that the information in Table 14 and the Pervier _et_ _al_. (1974) data are outdated.

3. From Transport and Storage

Transport and storage can release ECH to the environment through continuous or intermittent emissions, or discharges as the result of accidents. No information was available by which to quantify such releases to the environment.

Continuous emissions result from tank venting. Pervier and coworkers (1974) reported that atmospheric storage tanks which are used for ECH are unpadded and without vapor conservation devices. They did not estimate emissions from venting. Shell (1979) has estimated storage losses at 0.0005 pound of ECH per pound of production.

Table 14. Atmospheric Emissions from Glycerin (Glycerol) Plants using Epichlorohydrin and/or Allyl Chloride as Feedstocks (adapted from Pervier et al., 1974)

	PLANT I						
Capacity in Short Tons	47,500						
Description Diagram (Figure 2) Stream Designation	A	B	C	D	E	F	G
Emission (10^3 tons/ton glycerol)							
Allyl chloride	---	Included with propyl chloride	---	---	---	Included with propyl chloride	---
Isopropyl alcohol	---	---	---	1.665	---	0.4283	---
Iso- and n-propyl chloride	---	26.31	---	---	---	0.1681	---
1,2,3-Trichloropropane	---	---	---	3.269	---	---	---
2,3-Dichloropropene	---	---	---	---	---	---	---
Acrolein	---	---	---	---	---	---	---
Acetone	---	---	---	5.151	---	---	1.840
Hydrocarbon, unspecified (e.g., methane, ethane)	---	8.238	---	---	---	---	---
2,3-Dichlorohydrin	---	---	---	---	---	---	---
Epichlorohydrin	---	---	---	1.539	---	---	---
Emission control device	---	Scrubber	---	Scrubber	---	Scrubber	---

Table 14. Atmospheric Emissions from Glycerin (Glycerol) Plants using Epichlorohydrin and/or Allyl Chloride as Feedstocks (adapted from Pervier et al., 1974) (Cont'd)

	PLANT II							
Capacity in Short Tons	55,000							
Description Diagram (Figure 2) Stream Designation	A Hypochlorination Vent	B Hydrolyzer Vent	C EPI Lights Dist'n. Vent	D EPI Finishing Dist'n. Vent	E Glycerol Reactor	F Glycerol Evaporation Vent	G Glycerol Dist'n. Vent	H Glycerol Light Dist'n. Vent
Emission (10^3 tons/ton glycerol)								
Allyl chloride	---	---	0.1056	---	---	---	---	---
Isopropyl alcohol	---	---	---	---	---	---	---	---
Iso- and n-propyl chloride	0.01527	0.1717	0.1894	---	---	---	---	---
1,2,3-Trichloropropane	---	---	---	---	---	---	---	---
2,3-Dichloropropene	---	---	0.00972	0.002882	---	---	---	---
Acrolein	---	---	0.04284	---	Trace	---	---	---
Acetone	---	---	---	---	---	---	---	---
Hydrocarbon, unspecified (e.g., methane, ethane)	---	---	---	---	---	---	---	---
2,3-Dichlorohydrin	---	---	---	---	---	---	---	---
Epichlorohydrin	0.03627	0.02015	0.01332	0.1315	Trace	---	---	---
Emission control device	Jet Fume Scrubber	---	---	---	---	---	---	---

Pervier and coworkers (1974) estimated the ECH emissions from tank filling. Their estimate assumed that the vapor pressure and partial pressure are the same for atmospheric pressure storage. They suggested emissions as high as 50 lbs./hour with a vent concentration of 14% ECH in air.

Accidents can release hazardous levels to the environment. Information on a transportation related accident near Point Pleasant, West Virginia, was the only incident that has been described. No information was available on storage tank accidents discharging ECH.

The Point Pleasant accident occurred on January 23, 1978, when a tank car derailed, ruptured, and spilled 20,000 gallons (~197,000 lbs) of ECH. Because of immediate health and safety hazards, 400 persons were evacuated and the city's water plant was shut down (Anon., 1978a). The major concern was ground water contamination. The public water supply was drawn from wells at 25 feet depth, and the wells became heavily contaminated by the spilled ECH. Specific information is not yet available on the ECH concentration, the time required for self-cleaning (see Section III-A-1), or other salient details (Rosencrance, 1978).

The known details of the Point Pleasant spill demonstrate that transport accidents can occasionally result in a local hazard. No information was available upon which to predict the frequency of transport-related accidents.

Monitoring information on this spill is not yet available (Rosencrance, 1978). When it is released, the data will provide an estimate on hazards. Significant information is expected on the risk period to potable water as the result of a single, massive contamination of a water supply.

4. From Use

The discharge of ECH to the environment during use is most likely to occur as a result of volatilization. The emissions of ECH during glycerin manufacture were discussed in Section II-C-2, since the process uses crude ECH as an intermediate without isolating it. Emissions from glycerin manufacture were the only quantitative data. The remaining information on discharges from use are taken from monitoring reports (see Section II-E).

ECH has been monitored near factories in Russia. Fomin (1966) detected ECH in the atmosphere up to 200 meters from a factory, but did not specify whether it resulted from manufacturing operations or use. Lipina and Belyakov (1975) monitored ECH at a glycerin manufacturing plant, but information was not available on whether the feedstock was ECH or allyl chloride.

When epoxy resins were used for waterproofing the walls of pumping stations in an irrigation project at Uzbekistan, USSR, the air became contaminated with ECH (Danilov and Muratova, 1972). Pinchuk et al. (1969) found that the air inside a new five-story dwelling (in or near Moscow, USSR) constructed extensively of plastic materials was contaminated with ECH. The largest amounts of volatiles were given off by materials made from, among other things, epoxy cements. Lawrence and Autian (1972) suggested that epoxy resin volatiles (which may include ECH) are present in the atmosphere of small dental laboratories, where epoxy cements are used extensively. They also stated that these volatiles may alter the biological activity of medications the workers may be taking.

5. From Disposal

The generation and disposal of wastes from the manufacture of ECH and by glycerin production through ECH has been discussed and partially quantified (Gruber, 1976; Pervier et al., 1974). Although the studies have described waste stream composition and disposal methods, no information was presented on environmental discharge.

Gruber (1976) delineated the origin and composition of wastes generated by ECH production from allyl chloride. The overall process and its associated wastes are illustrated in the discussion on production methods (see Section II-A-3). The liquid heavy ends from a fractionating column at a 75,000 metric tons per year plant yield approximately 3,975 metric tons of organic waste which are described in Table 15. According to Gruber, these are not landfilled or encapsulated. The wastes are stored in large steel tanks in on-site facilities for eventual thermal destruction using controlled incineration. In addition, aqueous wastes from the separator contain dichloropropanol (0.01 ton per ton glycerol produced), but treatment of the aqueous waste was not described.

Pervier et al. (1974) described wastes from glycol manufacture. Two manufacturers (see Section II-C-2) described their waste generation and treatment. According to Pervier and coworkers, no discrete solid wastes form. Liquid wastes of 1200 and 1500 gallons per minute were generated in the two plants. No qualitative or quantitative information was available on ECH or other organic components of the waste. Waste water from glycerin production does not appear hazardous. Spencer (1971) reported a "very high" toxic threshold for aquatic organisms for the effluent from glycerin manufacturing plants.

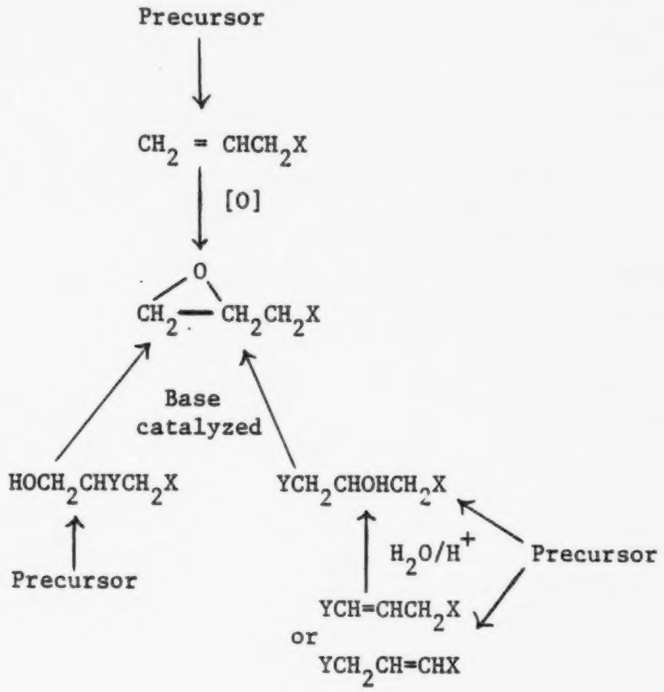
Shackelford and Keith (1976) listed frequency for chemicals observed in water; ECH was listed three times. Twice it was reported in effluent from an unspecified chemical plant in Louisville, Kentucky. Also, ECH was contained in one of several industrial waste filled drums which were dumped at sea near the coast of Holland (Grieve, 1971).

Table 15. Major Components of the Liquid Heavy Ends (Still Bottoms) from Epichlorohydrin Manufacture at a 75,000 Metric Ton per Year Plant (Gruber, 1976)

Component	Quality (metric tons per year)
1,2,3-Trichloropropane	2783
Tetrachloropropyl ethers	557
Dichloropropanol	425
Chlorinated aliphatics and alcohols	130
Epichlorohydrin	80
Water and unidentified products	100

6. Potential Inadvertent Production in Industrial Processes

Although no information was available on inadvertent production of epihalohydrins during industrial processes, numerous possible pathways were speculated based upon known reaction mechanisms (Gould, 1959). The flow chart delineates simple pathways by which precursors might be converted into epihalohydrins:


Precursor
CH2 = CHCH2X
[O]
O
CH2—CH2CH2X
Base catalyzed
HOCH2CHYCH2X
Precursor
YCH2CHOHCH2X
H2O/H+
Precursor
YCH=CHCH2X
or
YCH2CH=CHX

The epihalohydrins would most likely form from allylic halides or substituted propyl halohydrins. These could form in turn from other precursors. The industrial chemicals in Table 16 which would potentially be converted to the epihalohydrins were gathered from the Directory of Chemical Producers (SRI, 1977). Although reaction pathways could be devised for other propane derivatives, these are judged the most likely precursors for inadvertent epihalohydrin

Table 16. Potential Precursors for the Inadvertent Production of Epihalohydrins

---

Allyl chloride (3-chloropropene)
Allyl bromide (3-bromopropene)
2,3-Dichloropropene-1
1,3-Dichloro-2-propanol
1,3-Dichloropropene
2,3-Dibromopropanol
Tris(dichloropropyl) phosphate
Tris(dibromopropyl) phosphate
DBCP (dibromochloropropane)
Propylene glycol
Glycerin

---

production. These generalized pathways also describe inadvertent production in the environment (see Section II-A-7).

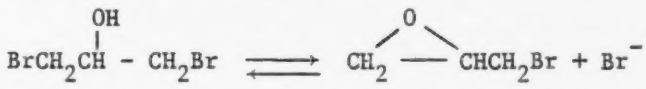
Allylic halides can be epoxidized by oxygen transfer agents such as peroxides (e.g., benzoyl peroxide) or metal oxides (e.g., copper or silver oxide). Catalytic oxidation of propane or propenes in the presence of halides could also yield epihalohydrins. The epihalohydrins could form from 1,2- or 1,3-dihalopropanols or other halopropanols by S_Ni (internal nucleophilic substitution) reactions (Gould, 1959). These halogenated propanols could either be commercial chemicals, such as 2,3-dibromopropanol, or produced from commercial chemicals. Examples of the latter would include hydration of 1,3-dichloropropene or hypochlorite addition to the allyl halides. Hypochlorite addition could be important if an industrial waste containing the allyl halide were chlorinated; this chlorination route will be discussed as a potential inadvertent production in the environment (see Section II-C-7).

The production and use of tris(halopropyl) phosphates, especially tris(dibromopropyl) phosphate and its precursor, 2,3-dibromo-1-propanol, are considered likely precursors for inadvertent epihalohydrin formation. 2,3-Dibromo-1-propanol is commercially manufactured by allyl alcohol bromination in aqueous lithium bromide (Clemons and Overbeek, 1966; Thomas and Levek, 1971). Although no information was available on the inadvertent production of EBH or its contamination of the commercial dibromopropanol, Great Lakes Chemical Corp. (1972) cautions that dehydrobromination to yield EBH could contaminate the product. Tris(dibromopropyl) phosphate is a fire retardant commercially produced by reacting dibromopropanol with phosphorous oxychloride in the presence of a tertiary amine base (Lande et al., 1976). Although epibromohydrin has not been reported as a by-product, base could conceivably catalyze the S_NI epoxidation. The use of tris(dibromopropyl) phosphate or tris(dichloropropyl) phosphate as a fire retardant for fabrics could also inadvertently produce epihalohydrin. However, the rate of production of these compounds has decreased considerably in recent years because of the mutagenicity of these fire retardants. The initial washing leaches these chemicals from the fabric; any hydrolysis within the alkaline wash waters will likely yield epihalohydrin. Since this is also a possible route for inadvertent production of epihalohydrins in the environment, further discussion is presented below (see Section II-A-7).

7. Potential Inadvertent Production in the Environment

Epihalohydrins could inadvertently form from biological or chemical transformations of halogenated propenes and propanols. The conceivable precursors are synthetic organic chemicals; however, no available evidence suggests that epihalohydrins form from naturally occurring organic chemicals. Some potential precursors listed above (Table 14) have been observed in water (Table 17) (Shackelford and Keith, 1976).

Epihalohydrins have been identified as intermediates in dibromopropanol metabolism (Bartnicki and Castro, 1969; Castro and Bartnicki, 1968). The conversion is an equilibrium process:



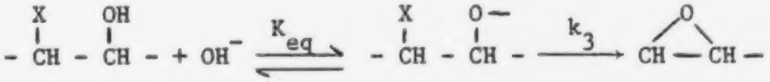
If chloride ion is present, ECH is also produced. Since the equilibria involved in epihalohydrin formation are closely related to transformations in their metabolic degradation, the subject is discussed in greater detail in the

Table 17. Observations of Potential Epihalohydrin Precursors in Water (Shackelford and Keith, 1976)

Compound	Source
Propanol, dichloro-	Seawater
Propanol, 1,3-dichloro-2-	Effluent from chemical plant
Propanol, 2,3-dibromo-1-	Effluent from chemical plants; effluent from landfills; well water
Propylene, dibromo	Effluent from chemical plant
Propylene, 1-chloro (allyl chloride)	Finished drinking water
Propylene, 1,3-dichloro	Finished drinking water

section on Biological Degradation, Organisms, and Products (see Section III-A-1-a).

Although no kinetic information was available which described chemical transformation of the precursor dihalopropanols to EBH or ECH in the environment, several studies on kinetics and mechanisms by which short-chained, aliphatic halohydrins cyclize to yield epoxides contain some useful data on the expected rates of epihalohydrin formation in water (Winstein and Lucas, 1939; Nilsson and Smith, 1933; McCabe and Warner, 1948; Winstrom and Warner, 1939; Stevens _et al_., 1948). These studies were primarily concerned with the mechanisms of reaction between halohydrins and base. The concensus is that the chlorohydrins and bromohydrins almost exclusively react with aqueous base to yield epoxide; direct hydrolysis of the halide to yield glycol does not compete. The reaction pathway has been described as the sequence:

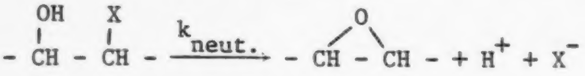


The kinetics have been well delineated. The alcohol-alkoxide equilibrium is fast and the rate determining step is ascribed to the S_Ni reaction of the halohydrin anion (k_3). The epoxide formation rate, dx/dt, is given by:

$$\frac{dx}{dt} = k_{OH}C_{HH}C_{OH^-}$$

where $k_{OH} = k_{eq}\ k_3$, and C_{HH} and C_{OH} - are the concentrations of halohydrin and hydroxide, respectively.

Nilsson and Smith (1933) published data that suggest a second path. In this alternative path, neutral halohydrin directly cyclizes to yield an epoxide:



$$-\overset{\mathrm{OH}}{\overset{|}{\mathrm{CH}}}-\overset{\mathrm{X}}{\overset{|}{\mathrm{CH}}}-\xrightarrow{k_{neut.}}-\mathrm{CH}\overset{\mathrm{O}}{-}\mathrm{CH}-+\mathrm{H}^{+}+\mathrm{X}^{-}$$

The overall rate, k_{obs}, must then contain contributions from both paths:

$$k_{obs} = k_{neut.} = k_{OH}C_{OH^-}$$

Although no rate data were available for the dihalopropanols, data have been published for epoxide formation from ethylene halohydrins, propylene chlorohydrins, and various derivatives of α,β-propylene chlorohydrins (Table 18). The rate constant increases observed with the addition of methyl groups have been ascribed to the relief of steric crowding as the bond angles open up during the epoxide formation (Gould, 1959). If this interpretation is correct, the minimum second order reaction rate (k_{OH^-}) must be about 2 l mole^{-1} mim^{-1} at 18° for the chloropropyl alcohol cyclization to epihalohydrin, and at least an order of magnitude faster (> 20 l mole^{-1} min^{-1}) for epihalohydrin for formation from the bromopropylalcohols (McCabe and Warner, 1948; Nilsson and Smith, 1933). Estimation of $k_{neut.}$ is more tenuous. The effect of the additional halide is assumed to affect epoxide formation rate mainly through steric effects. The relatively high rate for 2-chloro-2-methyl-1-propanol cyclization to the epoxide (0.00393 min^{-1}) at 18°) is taken as a reasonable estimate of the

Table 18. Kinetic Data for Epoxide Formation from Halohydrins in Water

Halohydrin	Temperature (°C)	k_{OH} ($l mole^{-1} min^{-1}$)	$10^2 k_{neut.}$ (min^{-1})
CH_2OHCH_2Cl	18	0.31 (estimate)[a]	---
	0	0.0167[b]	---
	15	0.153[b]	---
	25	0.600[b]	---
	35	2.17[b]	---
CH_2OHCH_2Br	0	0.987[b]	---
	5.0	2.03[b]	---
	10.0	3.95[b]	---
$CH_3CHOHCH_2Cl$	18	6.5[a]	---
$CH_3CHClCH_2OH$	18	1.7 (estimate)[a]	---
$(CH_3)_2COHCH_2Cl$	18	78[a]	---
$(CH_3)_2CClCH_2OH$	18	77[a]	0.393[a]
$(CH_3)_2CClCH(OH)CH_3$	18	633[a]	0.206[a]
$(CH_3)_2C(OH)CCl(CH_3)_2$	18	3600 (estimate)[a]	0.359[a]
$(C_2H_5)_2C(OH)CH_2Cl$	18	179[a]	
$(C_2H_5)_2CClCH_2OH$	18	358[a]	2.67[a]

[a] Nilsson and Smith, 1933
[b] McCabe and Warner, 1948

upper limit for chloropropyl alcohol cyclization. The rate of cyclization of 2-chloro-1-propanol is assumed to be the lower limit. If for k_{OH} and $k_{neut.}$ the relative ratios of 2-chloro-2-methyl-1-propanol:2-chloro-1-propanol are the same, then the lower rate limit is within a factor of 50, or $8 \times 10^{-5}\ \text{min}^{-1}$. The observed rate for epihalohydrin formation from the cyclization of chlorohalopropanol will then be given by:

$$k \approx 8 \times 10^{-5}\ \text{min}^{-1} + 2\ \text{lmol}^{-1}\ \text{min}^{-1}\ C_{OH^-}$$

Half-lives for epihalohydrin formation were estimated assuming constant pH. At neutral pH, epihalohydrins would form from chlorohydrin cyclization with an estimated $t_{1/2}$ of 6.0 days at 18° in water. At pH 9, $t_{1/2}$ would decrease to 4.8 days. Since ethylene oxide formation from ethylenebromohydrin reaction with caustic is more than an order of magnitude faster than from ethylene chlorohydrin (McCabe and Warner, 1948), then it is expected that precursor bromohydrins will yield epihalohydrins with $t_{1/2}$ of less than one day in water.

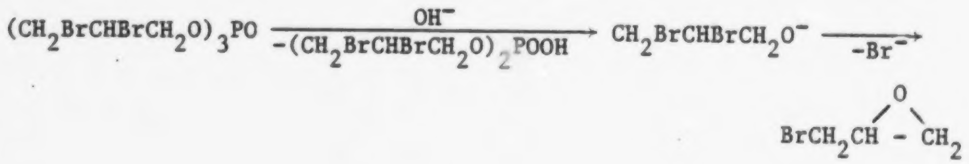
The precursor dihalopropanols can enter water directly or from other propane derivatives:

$$CH_2{=}CHCH_2X \xrightarrow{HOCl} ClCH_2CHOHCH_2X$$

$$CHX{=}CHCH_2X \xrightarrow{H_2O} XCH_2CHOHCH_2X$$

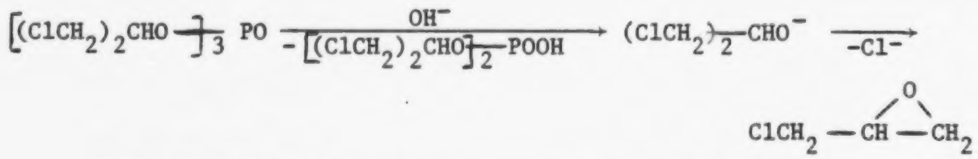
Chlorination of allylic halides in water treatment could yield 1,3-dihalo-2-propanols. The hydration of 1,3-dihalopropenes is possible only with acid catalysis and is unlikely under environmental conditions.

Hydrolysis of haloalkylphosphates is a potential source of epihalohydrin formation. These have been used as fire-retardants for clothing and other consumer items (see Section II-A-7). They are known to leach from fabric during laundering and might hydrolyze under alkaline conditions of washing (Lande et al., 1976). A potential sequence for epihalohydrin formation is:



$$(CH_2BrCHBrCH_2O)_3PO \xrightarrow[-(CH_2BrCHBrCH_2O)_2POOH]{OH^-} CH_2BrCHBrCH_2O^- \xrightarrow{-Br^-} BrCH_2CH \overset{O}{-} CH_2$$

or:



$$\left[(ClCH_2)_2CHO\right]_3 PO \xrightarrow[-\left[(ClCH_2)_2CHO\right]_2POOH]{OH^-} (ClCH_2)_2CHO^- \xrightarrow{-Cl^-} ClCH_2 - CH \overset{O}{-} CH_2$$

Although metabolic oxidation can convert olefins to epoxides (Williams, 1959), it is unlikely to produce epihalohydrins from allylic halides. Castro and Belser (1968) reported that allylic halides are hydrolyzed to allyl alcohol in soil by metabolic and chemical pathways.

D. Analytical Methods

The two general approaches that have been developed for determining epoxy compounds are wet chemical and instrumental methods, including chromatography. Interest in devising analytical methods for epoxy compounds developed in the late forties and has been primarily concerned with qualitative and quantitative methods suitable for quality control rather than for environmental monitoring.

The most common wet chemical method for the determination of compounds containing an epoxy ring involves ring opening by halogen acids to yield a halohydrin. While quantitative consumption of the hydrogen halide and formation of the halohydrin is the basis of the determination, there are many variations. One variation, which uses methyl ethyl ketone as the solvent and HCl as the acid, is claimed to provide good results for ECH (Dobinson et al., 1969).

Daniel and Gage (1959) determined ECH in prepared air samples with a colorimetric method involving oxidation of ECH with periodic acid followed by the reaction of the formaldehyde produced with ammonia and acetylacetone to give a yellow color. Levels of ECH down to about 6 ppm could be determined with an error of about 2%. Similar procedures have been reported by Gronsberg (1961, 1966), Pimenova and Khamaza (1962), Jaraczewski and Kaszper (1967), Krynska (1968, 1973), Fomin (1976), and Stanislav (1976). These latter papers were published in Russian or Polish. Gronsberg (1961) reports a sensitivity for his method of about 6 ppm.

Ring opening methods by sulfur-containing nucleophilic reagents such as sodium thiosulfate or sodium sulfite are particularly useful with ECH, which is generally more reactive with those reagents than other epoxides. The presence of the electron withdrawing group $ClCH_2$- is responsible for the greater reactivity of ECH. An extensive collection of halogen acid and sulfur nucleophile ring opening methods has been summarized by Dobinson et al. (1969). Unfortunately, sensitivity data were not provided.

Mismash and Meloan (1972) described an indirect spectrophotometric method for all types of oxiranes which involves hydrolysis to glycols, followed by cleavage with excess periodate. The technique is said to be sensitive to the nanomole range, but data for ECH and EBH are not given.

The use of infrared spectroscopy as an analytical tool for epoxides was first explored by Geddu and Delker (1958). The sharp absorbances exhibited by terminal epoxides at 1.65 and 2.2 mμ can be used to determine these compounds down to about 10 ppm of terminal epoxy ring with an accuracy and precision on the order of ±2%. The major advantage of IR over chemical methods is that it is very fast. Terminal olefins, which absorb in the same regions, can interfere.

In recent years more advanced techniques have been applied to the determination of epihalohydrins, although the emphasis has been on qualitative methods rather than the quantitative techniques essential for good monitoring studies. For example, photoelectron spectroscopy can be used to distinguish qualitatively EBH, ECH, epifluorohydrin, and other halo-oxygen compounds (Baker _et_ _al_., 1971). Photoelectron spectroscopy is not suitable for quantitative studies.

Muganlinskii and coworkers (1974) worked on analytical procedures by gas chromatography primarily to identify and quantify impurities contained in technical ECH. Their optimum analytical procedure used a 3 m by 4 mm diameter column packed with 20% polyethylene glycol 1540 on diatomaceous brick (0.25-0.5 mm). Operating conditions included: injector port temperature of 200°; carrier gas (hydrogen) flow rate of 80 ml/min; column temperature was linear programmed between 50 and 130°C at 7°/min. Ten μl samples were used with thermal conductivity detection. The retention times for ECH and components of the technical material which could potentially interfere with the ECH peak are as follows: chloroform (2.2); 1,2-dichloropropane (2.47); 2,3-dichloropropene (2.67); ECH (3.04); and trichloropropane (5.10). They did not publish any useful data on sampling.

The National Institute for Occupational Safety and Health (NIOSH) method (NIOSH, 1976; White et al., 1970) describes sampling and gas chromatographic (GC) analysis for measuring ambient atmospheric concentration of ECH. The method requires sampling with standard commercial charcoal tubes. The tubes are glass and have the dimensions 7 cm long by 6 mm OD and 4 mm ID. They are packed with 150 g of 20/40 mesh activated charcoal separated by 2 mm of polyethylene foam into two sections: 100 cm in front and 50 cm in the rear. The NIOSH method will allow samples as large as 20 l collected at 200 ml/min. The sample tubes are then capped (plastic) until analysis. The organics are desorbed from each charcoal section with 1.0 ml of carbon disulfide for 30 minutes; the front and rear sections are to be separately analyzed. Samples of 5.0 μl of the carbon disulfide solution are analyzed by GC using a 10 foot by 1/8 inch stainless steel column packed with 10% FFAP on acid washed DMCS chromosorb W (80/100). Conditions are 200° injector port, 230° detector (flame-ionization), 135° column, and carrier gas (helium) at 20 ml/min. The overall method will reportedly operate over the concentration range 11.7 - 43.1 mg/cu m of ECH. At an ECH concentration of 5 ppm (18.9 mg/cu m), the relative error was 0.7%. NIOSH (1976) reported that the method can be used down to 0.25 μg/l. No specific lower detection limit or sensitivity was reported for the GC analysis of the charcoal desorption. The estimated efficiency of the charcoal desorption step was 82.7% after 14 day tube storage. Over 90% efficiency was achieved for the upper end of the working range for sample desorption if the tubes were desorbed soon after samples were collected.

The West Virginia Health Department Laboratory has developed a method which uses GC for quantitative analysis of aqueous ECH (Rosencrance, 1978). The method was developed to monitor ECH contaminated waters as the result of the transportation related spill at Point Pleasant, West Virginia (see Section II-C-3). Experimental details are not yet available.

The analytical methods described above are summarized in Table 19. Lower detection limit and analytical error are estimated.

E. Monitoring

Pervier and coworkers (1974) have published some information gathered from manufacturers on atmospheric emissions of ECH and other chemicals from glycerol manufacturing plants (see Section II-C-2). Although it is not known how the manufacturers derived the information, monitoring was one likely source.

No quantitative monitoring information was available on ambient ECH or EBH concentrations in the environment. The only monitoring information available for the U.S. was its observation in effluent from an unspecified chemical plant in Louisville, Kentucky (Schackelford and Keith, 1976).

The remaining monitoring data available for ECH is based on work done in the Soviet Union, where it has been monitored in the atmosphere in the vicinity of factories which manufacture epoxy resins and glycerin, as well as in plants producing ECH.

In a study of the ECH manufacturing industry in Russia, Pet'ko _et al_. (1966) found ECH in atmospheric samples taken from the working area. Of 206 samples, the ECH concentration was below the permissible level (0.05 ppm) "in only a very few of the tests, and in some instances exceeded the maximum permissible limit by a factor of 2-14 times." Hydrogen chloride was also found in high concentrations. Although it isn't possible to extrapolate these findings to manufacturing conditions in the U.S., this study does establish the potential

Table 19. Summary of Analytical Methods for Epihalohydrins

Technique	Compound	Approximate Lower Detection Limit	Error	Source
Colorimetric	ECH	∿6 ppm	∿2%	Daniel and Gage, 1959
Colorimetric	ECH	8 ppm		Gronsberg, 1961
Infrared	ECH	∿10 ppm	± 2%	Geddu and Delker, 1958
Gas-Liquid Chromatography	ECH	(50 ppb in 20 1 atmospheric samples)	0.7% for 5 ppm in 20 1 atmospheric samples	NIOSH, 1976
Miscellaneous Chemical Methods				Dobinson _et al_., 1969

atmospheric contamination near ECH plants in the U.S. It was reported that tank filling and transferring operations were particularly liable to give rise to contamination in the immediately surrounding air (see Section II-C-3).

In a pollution study of a factory which discharged ECH to the atmosphere, 0.1-3 ppm of the chemical was monitored within 100-200 meters of the factory (Fomin, 1966). At 400 meters, five of 29 samples exceeded the author's recommended maximum permissible level of 0.05 ppm.

Pinchuk et al. (1969) detected ECH in the atmosphere of a building whose construction employed extensive use of plastic materials. Epoxy cements were reported to be the main source. Danilov and Muratova (1972) found that when epoxy resins were used for waterproofing the walls of a pumping station, the air became polluted with ECH.

Lipina and Belyakov (1975) found ECH in the air of a glycerin manufacturing plant, along with allyl alcohol and allyl chloride. Specific data as to the ECH concentrations measured were not given in the translated abstracts examined.

Although no specific mention is made concerning monitoring water, a paper by Fedyanina (1968) on the effect of ECH in water on rats, rabbits, and guinea pigs, as well as the inclusion of human taste and irritation data, made statements which suggest that ECH has been monitored in tap water in Russia. Fedyanina found that 30% of the initial amount of ECH placed in water samples remained after seven days (see Sections I-B-2 and III-A-1-b). Whether the tap water was quiescent and/or in contact with air is not indicated.

A summary of the monitoring of ECH in the Soviet Union is listed in Table 20.

Table 20. Atmospheric Monitoring of Epichlorohydrin in the Soviet Union

Source	Reference
Epichlorohydrin manufacturing plant	Pet'ko _et al_., 1966
Factory (type not specified)	Fomin, 1966
Newly constructed housing	Pinchuk _et al_., 1969
Glycerin manufacturing plant	Lipina and Belyakov, 1975

III. Health and Environmental Effects

A. Environmental Effects

1. Persistence

a. Biological Degradation Organisms and Products

The epihalohydrins have been identified as intermediates in the enzyme catalyzed hydrolysis of 2,3-dibromo-1-propanol (Section II-C-7). This was the only work available on microbial degradation (Castro and Bartnicki, 1968; Bartnicki and Castro, 1969). The salient information was limited to product and qualitative reaction rate studies with enzyme extracts of gram-negative Flavobacterium sp.

The Flavobacterium sp. was collected from an alfalfa field soil and grown in an aqueous broth containing 5 x 10^{-3} M dibromopropanol. The enzyme was extracted from the cells by a combination of centrifugation and sonication. The enzyme activity in the extracted solution was equivalent to activity of the bacterium cell suspension. The crude enzyme extract was partially purified, precipitated, and part of the protein fraction was placed onto Sephadex G-200.

Dibromopropanol, the epihalohydrins, and epihalohydrin hydrolysis products were metabolized with the crude enzyme extract and the partially purified enzyme at pH 7. If the enzyme solution was boiled, its hydrolysis activity was lost. The earlier study (Castro and Bartnicki, 1968) demonstrated that 2,3-dibromo-1-propanol is initially converted to epibromohydrin. The subsequent reactions depend, in part, upon the added salt (KCl or KBr). Table 21 summarizes products and rates for reactions of the epihalohydrins and their degradation products; these data were derived from incubation of 10^{-3} M substrate in 10 ml of a 0.02 M phosphate buffer (pH 7.0) and

Table 21. Products from Enzymatic Conversion of Epihalohydrins and Haloalcohols (Bartnicki and Castro, 1969)

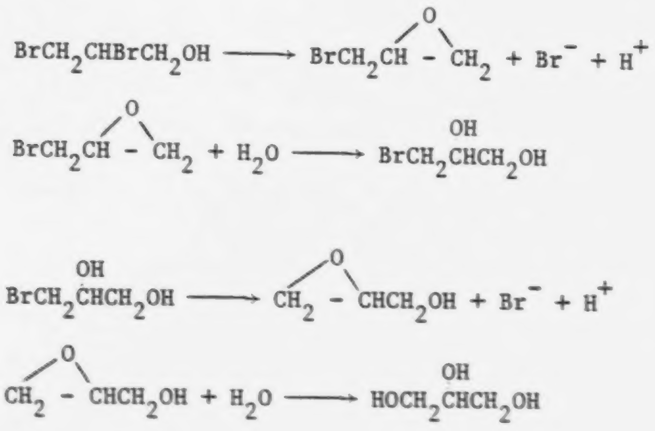
Substrate	Added Salt (0.1 M)	Time (min)	% Conversion	Products (% yield)[a]
Epibromohydrin	KCl	1	7.4	1-Bromo-3-chloro-2-hydroxypropane[b]
	KCl	60	100	1,3-Dichloro-2-hydroxypropane, 1-chloro-2,3-dihydroxypropane, 1-bromo-2,3-dihydroxypropane
	KBr	1	2.0	1,3-Dibromo-2-hydroxypropane
	KBr	60	95	1-Bromo-2,3-dihydroxypropane, glycidol (trace)
	None	1	1.7	1-Bromo-2,3-dihydroxypropane
	None	60	81	1-Bromo-2,3-dihydroxypropane, glycidol (trace)
Epichlorohydrin	KCl	1	1.6	1,3-Dichloro-2-hydroxypropane
	KCl	60	100	1,3-Dichloro-2-hydroxypropane, 1-chloro-2,3-dihydroxypropane
	KBr	1	1.2	1-Bromo-3-chloro-2-hydroxypropane
	KBr	60	60	1-Chloro-2,3-dihydroxypropane, 1-bromo-2,3-dihydroxypropane, epibromohydrin
	None	1	0.4	1-Chloro-2,3-dihydroxypropane
	None	60	31	1-Chloro-2,3-dihydroxypropane
1-Bromo-3-chloro-2-hydroxypropane	None	5	30	Epichlorohydrin (85), epibromohydrin (15)
	None	120	100	1-Chloro-2,3-dihydroxypropane (86), 1-bromo-2,3-dihydroxypropane (14)
1,3-Dibromo-2-hydroxypropane	None	1	10	Epibromohydrin
1,3-Dichloro-2-hydroxypropane	None	10	50	Epichlorohydrin
		30	69	1-Chloro-2,3-dihydroxypropane, epichlorohydrin

---

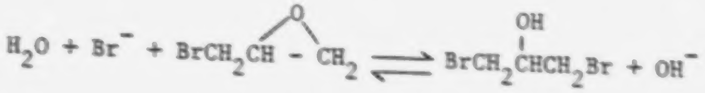
[a] Where yields are not given, products are listed in a decreasing order of significance. Yield = (moles of product/moles of substrate converted) 100.

[b] Yields of all single products are 100%.

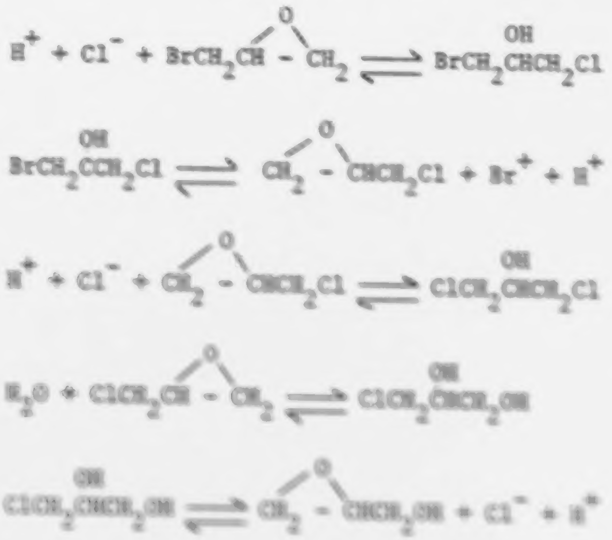
0.25 mg of protein thermostated at 24°C. The hydrolysis of 2,3-dibromo-1-propanol followed the reaction sequence:



Bromide ion can open the epoxide to yield 1,3-dibromopropanol (see Section I-B-1):



Incubation with the addition of 0.1 M KCl establishes the following equilibrium:

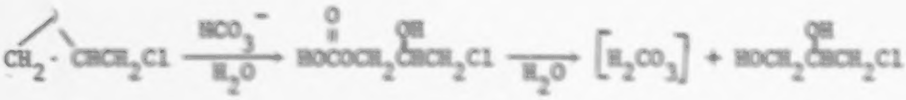


In summary, the epihalohydrins appear susceptible to metabolic hydrolysis in soil. Products vary as the result of the ionic content of the media and the metabolic transformations parallel chemical reactions (see Section I-B-10). Metabolic reaction rates in soil were not available.

b. Chemical Degradation in the Environment

The epihalohydrins will chemically degrade in the environment. The initial chemical reactions are discussed in Section I-B.

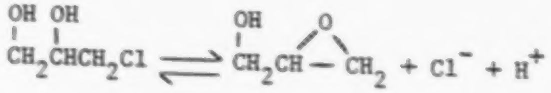
The hydrolysis and related reaction rates and products depend upon the ionic content of the water. Reaction with water to yield 1-halo-2,3-propanediols will compete with anion reactions to open the epoxide and yield the corresponding 1-substituted-3-chloro-2-propanols. While some anions (such as chloride) yield products which are stable enough to isolate, others (such as bicarbonate or nitrate) yield transient products. For example, the bicarbonate adduct, which is the monocarbonate ester of 3-chloro-1,2-propanediol, rapidly hydrolyzes (Shvets and Aleksanyan, 1973):



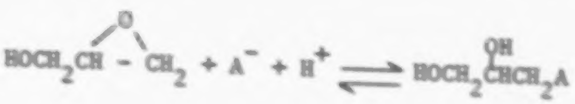
$$CH_2\cdot CHCH_2Cl \xrightarrow[H_2O]{HCO_3^-} HO\overset{O}{\overset{\|}{C}}OCH_2\overset{OH}{C}HCH_2Cl \xrightarrow[H_2O]{} [H_2CO_3] + HOCH_2\overset{OH}{C}HCH_2Cl$$

So, bicarbonate and other anions which yield transient intermediates are catalysts for hydrolysis to halopropanediols. As Section I-B-1 described, the maximum hydrolysis half-life for ECH at 20°C is 8.0 days in CO_2-free, distilled water. A change in pH down to pH 4 is expected to alter the hydrolysis rate only slightly (an increase less than 5%), but not to affect products. The ECH half-life in CO_2-free water containing 3% NaCl (approximation for sea water) was calculated as 5.3 days, and the resulting ratio of 1-chloro-2,3-propanediol:1,3-dichloro-2-propanol was calculated as 2.0. Dissolved carbonate is expected to reduce the ECH half-life and increase the proportion of 1-chloro-2,3-propanediol as the result of bicarbonate and carbonate catalyzed hydrolysis.

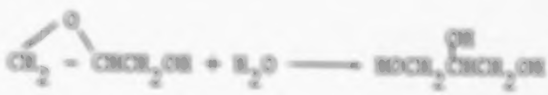
The initial hydrolysis products are expected to react further at first to yield a new epoxide. The most important reaction will be formation of glycidol.



Products formed by anion attack on this epoxide can yield a new halohydrin (Section II-C-7, "Potential Inadvertant Production in the Environment"):



Because chloride is probably the most common anion, the most likely reaction of this type is the back attack of chloride in the equilibrium reaction. The most significant reaction of glycidol is its hydrolysis to yield terminal product glycerin:



The rates for glycidol formation from the chloro- and bromopropanediols are expected to be similar to rates of EBH and ECH formation from the dihalopropanols (see Section II-C-7). So, it is reasonable to expect half-lives of about 6 days and less than 1 day for chloropropanediol and bromopropanediol, respectively, in water at 18°.

The epihalohydrins are expected to degrade rapidly in air by free-radical reactions of the photochemical smog cycle (Dilling _et al._, 1976). ECH appears to degrade very rapidly, and it is expected that EBH will also rapidly be degraded. Products are unknown (see Section I-B-3).

2. Environmental Transport

Although no direct information was available on the environmental transport of the epihalohydrins, transport characteristics can be estimated from physical properties (Table 2). Sufficient information is available to delineate the transport of ECH, but insufficient data on solubility and vapor pressure are available for reasonable approximation on EBH.

ECH is water soluble (about 66 g/l) and volatile (about 80 torr at 55.2°C). These values indicate that ECH can be transported as a vapor in the atmosphere and in solution in water.

The evaporation half-life was estimated by the method of Dilling (1977). The evaporation half-life, $t_{1/2}$, is calculated as:

$$t_{1/2} = \frac{0.6931d}{K_L}$$

where d is water depth in cm. Calculation of the exchange constant, K_1 requires the Henry's law constant, H, and molecular weight, M:

$$K_1 = \frac{221.1}{(\frac{1.042}{H} + 100.0)M^{1/2}}$$

The vapor pressure at ambient temperature must be known for calculation of H. Since vapor pressure data for ECH at ambient temperature was not available, vapor pressure was assumed as 15 torr at 20°. This assumption is probably within a factor of 2 of the actual value and will provide a reasonable, qualitative estimate. Henry's law constant, H, was calculated by the equation:

$$H = \frac{16.04\ MP}{TS}$$

where M is the molecular weight (92.53 g), P is the pressure (15 torr), T is the absolute temperature (293°K), and S is the solubility $65.2 \times 10^{[illegible]}$ ppm). These values yielded $H = 11.8 \times 10^{-4}$. The exchange constant, K_1, was calculated as 0.023 min^{-1} and $t_{1/2}$ as 30d (d = depth in cm). For a 1 m depth of water, evaporation half-life is about 2.1 days at 20°C.

No information was available concerning epihalohydrin sorption with aquatic sediment or soil, nor were any data found concerning all transport processes.

3. Bioaccumulation and Biomagnification

Laboratory or field studies on the bioaccumulation and biomagnification are not available. While ECH solubility data permit its assessment, the lack of data precludes any such attempt for EBH.

The bioconcentration factor (BF) was calculated by the method of Neely _et_ _al_. (1974):

$$\log BF = 0.542 \log K + 0.124$$

where K is the _n_-octanol:water partition coefficient. BF is a measure of the expected concentration of an organic chemical in tissue based upon its solubility in fat. A partition coefficient of about 10 for ECH was extrapolated from a graphed relationship between K and water solubility (Freed and coworkers, 1977). The calculated BF was approximately 4.6 (log BF = 0.666). This is a relatively low value, which indicates that bioaccumulation in the environment is not likely.

B. Biological Effects

1. Toxicity and Clinical Studies in Man

a. Occupational Studies

In the industrial setting, ECH is well-known for its ability to irritate the eyes, skin, and respiratory tract upon contact with vapor or liquid (NIOSH, 1976, 1977; ACGIH, 1977). In addition, systemic absorption may occur by passage of ECH across the respiratory epithelium or the skin to result in gastrointestinal disturbances, pain in the region of the liver, labored breathing, cough, cyanosis, and chemical pneumonitis. ECH has been implicated in the allergic contact dermatitis associated with the handling of epoxy resins (Hamilton and Hardy, 1974), although its role as a causative agent has been discounted (NIOSH, 1976; Nater and Gooskens, 1976; Askarova and Muryseva, 1976). No cases of death in humans have been reported to result from direct contact with ECH.

There has been little evidence in the past to suggest that worker populations as a whole may be adversely affected by exposure to ECH. Pet'ko and coworkers (1966) examined the health of 82 persons (49 men and 33 women, primarily in the 20-35 age range) engaged in the production of ECH from dichlorohydrin glycerin. Although average exposure levels were not reported, isolated exposures sometimes reached 19-21 mg/m^3 (approximately 4.9-5.5 ppm), and emergency conditions resulted in levels of 210-211 mg/m^3 (approximately 54.6-54.9 ppm). Several parameters of health were examined such as: days lost due to illness; condition of the ocular mucous membranes, skin, respiratory organs, cardiovascular system, and nervous system; peripheral blood morphology; reticulocyte count; bilirubin and cholesterol levels; blood protein fractions;

respiratory function; and general urinalysis. It was concluded that no deviations from the normal could be identified, with the possible exception of two cases of occupational dermatitis.

NIOSH (1976) has summarized the results of a morbidity study involving 48 persons, presumably employed by the Dow Chemical Company, having at least one occupational exposure to ECH. Blood chemistry determinations, hematocrit index, and total and differential leukocyte counts were made. In 39 of the 48 workers, most determinations of percent polymorphonuclear leukocytes were below normal; determinations of percent of monocytes were mostly above normal for 35 of the employees. Both the leukocyte and monocyte changes were common to 32 of the 48 employees, and might thus have been related. Other abnormalities found included: majority of determinations of percent eosinophilic leukocytes above normal in 16 employees; total leukocyte counts and hemoglobin concentrations increased in 15 employees; decreased total leukocytes and hemoglobin levels in five and eight employees, respectively; and decreased blood SGOT activity in 13 employees. Most of these deviations from normal were no longer detectable after a few months removal from exposure.

In a related morbidity study conducted in Russia, workers (number unspecified) exposed to ECH at levels of 0.23-3.1 mg/m^3 (approximately 0.06-0.8 ppm) were examined for adverse health effects (Kovalenko and Bukav, 1975). The authors reported that an increased phagocytic activity of the leukocytes was observed, which apparently resulted as an adaptive effect.

The potential importance of ECH as an occupational health hazard has been greatly underscored by recent cytogenetic studies conducted on workers exposed to ECH. A series of reports from investigators in Czechoslovakia and Russia (Kucerova, 1975, 1976; Kucerova et al., 1976, 1977) established that chromosome changes occur in human lymphocytes exposed to ECH either in vitro or in vivo. Initial studies with cultured human lymphocytes exposed to ECH for 24 hours at concentrations ranging from 10^{-4} to 10^{-1} M established that dose-dependent chromosome damage could occur (Kucerova et al., 1976). Chromatid breaks and chromosome breaks were the most common aberration; chromatid exchanges and chromosomal exchanges were rare (Table 22). The distribution of ECH-induced breaks was nonrandom, and suggested that certain segments of the chromosomes were more sensitive to damage than others (Kucerova and Polivkova, 1976). The potency of ECH was considerably less than that of the strong mutagen, tri(1-aziridinyl)-phosphine oxide (TEPA).

In a subsequent study, 35 workers (23 to 34 years of age) occupationally exposed to ECH were examined for chromosomal aberrations in their lymphocytes (Kucerova et al., 1977). Blood samples were taken from the workers both before and after they had been exposed to ECH on the job. Lymphocytes were cultured for 36 to 58 hours prior to analysis. ECH exposure in these workers ranged from 0.5 to 5.0 mg/m^3 (approximately 0.13 to 1.3 ppm). Cytogenetic analyses revealed that the percentage of aberrant cells collected before the start of ECH exposure did not differ from that in other normal human populations. However, blood samples taken after one and two years of exposure showed increasing numbers of cells with chromosome defects (Table 2). In accordance with the results of earlier in vitro tests, chromatid and chromosomal breaks were the most frequent aberration observed. Although the authors indicated that the workers had not been concurrently exposed to radiation or other known mutagens, it is not known to what extent

Table 22. Mutagenic Effect of Epichlorohydrin and TEPA in Different Concentrations[a] (Lymphocytes exposed to epichlorohydrin (ECH) and TEPA during last 24 hours of cultivation.)

	Number of cells scored	Cells with aberrations		Type of aberration				Number of aberrations per 100 cells	Number of breaks per 100 cells	Number of gaps
		number	(%)	Number of chromatid breaks	Number of chromatid exchanges	Number of chromosomal breaks	Number of chromosomal exchanges			
ECH [illegible]	[illegible]	[illegible]	[illegible]	[illegible]	1	13	2	8.9	9.7	8
ECH [illegible]	[illegible]	[illegible]	[illegible]	[illegible]	0	2	0	3.3	3.3	5
ECH [illegible]	[illegible]	[illegible]	[illegible]	[illegible]	0	4	0	3.0	3.0	5
ECH [illegible]	[illegible]	[illegible]	[illegible]	[illegible]	1	1	0	1.3	2.3	2
ECH [illegible]	[illegible]	[illegible]	[illegible]	[illegible]	1	1	0	1.0	1.3	3
ECH [illegible]	[illegible]	[illegible]	[illegible]	[illegible]	1	0	1	1.7	2.3	0
ECH [illegible]	[illegible]	[illegible]	[illegible]	[illegible]	0	1	0	0.7	0.7	1
TEPA [illegible]	[illegible]	[illegible]	[illegible]	[illegible]	11	68	0	89.0	95.0	103
TEPA [illegible]	[illegible]	[illegible]	[illegible]	[illegible]	4	43	2	68.5	51.5	15
TEPA [illegible]	[illegible]	[illegible]	[illegible]	[illegible]	1	25	0	14.0	14.3	15
TEPA [illegible]	[illegible]	[illegible]	[illegible]	[illegible]	0	4	1	3.0	4.2	3
TEPA [illegible]	[illegible]	[illegible]	[illegible]	[illegible]	0	6	1	4.0	4.3	4
TEPA [illegible]	[illegible]	[illegible]	[illegible]	[illegible]	0	2	0	1.7	1.7	1
TEPA [illegible]	[illegible]	[illegible]	[illegible]	[illegible]	0	2	0	2.3	2.3	2
TEPA [illegible]	[illegible]	[illegible]	[illegible]	[illegible]	2	5	1	3.0	3.7	3
Control	[illegible]	[illegible]	[illegible]	[illegible]	0	1	1	0.7	0.9	7
Control with DMSO	[illegible]	[illegible]	[illegible]	[illegible]	0	[illegible]	0	1.0	1.0	0

[a] [illegible]

Table 23. Chromosomal Analysis of Workers Occupationally Exposed to Epichlorohydrin[a] (summarized results from Prague and Moscow)

Number of persons	Number of cells scored	Cells with aberrations		Types of aberration				Number of aberrations (per 100 cells)	Number of breaks (per 100 cells)	Number of gaps (per 100 cells)
		Number	%	Number of chromatid breaks (per 100 cells)	Number of chromatid exchanges (per 100 cells)	Number of chromosome breaks (per 100 cells)	Number of chromosome exchanges (per 100 cells)			
20 1st collection (controls)	5050	69	1.37	49 (0.97)	3 (0.06)	14 (0.28)	6 (0.12)	72 (1.42)	81 (1.60)	19 (0.38)
20 2nd collection	5445	106	1.94	57 (1.05)	6 (0.11)	33 (0.61)	8 (0.15)	104 (1.91)	118 (2.17)	49 (0.90)
20 3rd collection	6175	165	2.67	100 (1.62)	6[b] (0.10)	64 (1.06)	13 (0.21)	188 (2.96)	201 (3.26)	64 (1.04)

[a] From Kucerova et al., 1977

[b] One chromatid exchange was [illegible]-union, therefore, it was calculated as only one break.

Difference between 1st and 2nd collections: $\chi^2_1 = 5.0$, $P = 0.025$; significant difference.
Difference between 2nd and 3rd collections: $\chi^2_1 = 8.0$, $P = 0.005$; significant difference.
Difference between 1st and 3rd collections: $\chi^2 = 26.0$, $P < 0.0001$; highly significant difference.

simultaneous exposure to other chemicals in the workplace may have affected the results.

In the United States, a recent report has also linked occupational ECH exposure to chromosome damage among workers (Picciano, 1979). In a group of 93 epoxy resin workers exposed to ECH at levels below 5 ppm an excess of chromosome abnormalities was found in their peripheral lymphocytes when compared to 75 controls. The incidence of abnormalities was approximately double that found in control workers having no ECH exposure. The possibility of simultaneous exposure to chemicals other than ECH must be considered, however, in evaluating these results. In addition, it was noted that the production of chromosome abnormalities may be a reversible effect, and thus its ultimate health impact is unclear.

These data on ECH-exposed workers in the United States were expanded and further analyzed by Barna-Lloyd et al. (1979) at Dow Chemical. They presented cytogenetic data on a group of 76 epoxy resins workers compared with 26 controls and on a group of 115 glycerine workers compared with 37 controls. It is not known to what extent this study overlaps with that reported by Picciano (1979). Levels of chromosome aberrations were apparently elevated in the epoxy resins workers but not among the glycerine workers when compared to the control group. The eleveated levels of damage in the epoxy resins group were reduced when retested eight months later.

Both the Picciano et al. (1979) study and the Barna-Lloyd et al. (1979) study suffer from a similar methodologic drawback in that reliance was placed on external control groups for comparison rather than upon the preferable method of using pre-exposure determinations in the same individuals. It should be noted that the Kucerova et al. (1977) study summarized above, pre-exposure determinations were employed.

The significance of cytogenetic analysis of human chromosomes is claimed to be for the indication of increased cancer risk and possible transmission of birth defects and mutations from one generation to the next. On the other hand, it is often stated that there is no a priori reason why neoplastic transformation or mutagenesis should involve any kind of visible chromosome damage (Kucerova, 1976). One can argue that the induction of point mutations, a process which is consistent with chemical carcinogenesis, occurs without gross chromosome damage. Moreover, the use of somatic cells to predict a mutagenic effect that might occur in germinal cells may have limited validity. Nevertheless, numerous examples of the positive correlation between a chemical's ability to produce chromosome aberrations in somatic cells and its carcinogenic/mutagenic activity indicate that cytogenetic data should be carefully evaluated.

The most recent study concerning health impairment among ECH workers at Dow Chemical examined potential effects on male fertility (Venable and McClimans, 1978). Sperm counts taken from 128 volunteers showed no variation from that of a control group, although a lower percentage of motile sperm was found in the ECH-exposed group. Similarly, measurements of hormone levels in these workers did not differ significantly from controls (method for selection of controls not specified). Sperm counts did not correlate either to the duration or intensity of exposure to ECH. However, ECH is suspect as a reproductive hazard on the basis of animal data which indicate an antifertility effect in males (see Section III.B.2.f).

b. Poisoning Incidents and Case Histories

Cases of acute intoxication by ECH have only infrequently been reported in the scientific literature. In Germany, Schultz (1964) published a case report concerning a 39 year old worker exposed to a single gust of ECH. The immediate reaction to exposure was eye and throat irritation, followed by facial swelling, nausea, vomiting, headache, and dyspnea. Subsequent clinical examinations revealed an enlarged liver accompanied by jaundice. Five months after the incident, liver damage and abnormal liver function were found along with bronchitic alterations in the right lung and elevated blood pressure. Even after two years, liver function remained abnormal and chronic asthmalike bronchitis was present.

NIOSH (1976b) reported the case of a 53-year-old worker exposed to ECH fumes for about 30 minutes whose symptoms resembled those in the case presented above. However, recovery from the exposure was rapid and complete, with the exception of recurrent infections of the upper respiratory tract. Since the intensity of ECH exposure was not known, it is not possible to relate specific effects to the amount of ECH absorbed.

The adverse effects of ECH resulting from contact with the skin and the respiratory and conjunctival mucosae have been well documented. NIOSH (1976b) summarized data indicating that a concentration of 20 ppm ECH causes a transient burning of the eyes and nasal mucosa. At a concentration of 40 ppm, ECH produces eye and throat irritation which persists for 48 hours. Concentrations of ECH in excess of 100 ppm are considered intolerable, even for brief periods. In addition it was stated that lung edema and kidney lesions may result with concentrations of ECH at 100 ppm in air.

Several detailed accounts of workers receiving skin burns as a result of contact with ECH were published by Ippen and Mathis (1970) in Germany. A common observation among the five cases studied was that the appearance of symptoms (redness, swelling, itching, burning) was usually delayed. In one case, two days passed before symptoms were noted. The intensity of skin reaction to ECH varied, although it was not possible to relate the degree of exposure to the effect produced. In the mildest cases, severe redness, swelling, itching, and red papules appeared on the hands or legs, which required treatment lasting up to several weeks. In more severe cases, ECH caused blisters and severe skin erosion accompanied by lymph node enlargement.

c. Epidemiology

Detailed epidemiologic studies on ECH have not been reported in the scientific literature. However, two studies conducted on ECH workers have recently been summarized. In the first, a retrospective examination of morbidity among 507 Dow Chemical Company employees was conducted (Hine, 1976). Most of the workers were exposed to ECH for five years or less, although exact numbers and quantitative exposure data were not given. In addition, there was no defined sampling scheme reported either for initial selection of individuals or for subsequent measurements. A medical examination of the workers revealed no apparent abnormalities in blood chemistry or liver and kidney function. However, episodes of illness due to respiratory problems were judged to occur more often when ECH workers were compared in exposure and non-exposure situations. In addition, employees having the greatest exposure to ECH also showed slight elevations in the white blood cell count and wide fluctuations in the monocyte cell count. The lack of a control group prevented a critical comparison of clinical and laboratory findings in ECH workers to those of a normal population. The more appropriate units of comparison would have been an individual's hematologic values upon entry into employment and the same individual's values after exposure to ECH. Furthermore, this study has little value in the assessment of many chronic diseases, including cancer; insufficient time had elapsed for such effects to be expressed, and workers who dropped out of the study due to illness, retirement, or death were not considered.

A mortality study was conducted on 864 active and retired Shell Chemical Company workers exposed to ECH for at least six months during the period from 1948 to 1965 (Enterline and Henderson, 1978; Enterline et al., 1979). Mortality information was gathered on the entire cohort through 1977. This report is the first to suggest a possible carcinogenic risk for workers exposed to ECH. Out of a total of 52 deaths in this cohort, nine (17.3%) were due to respiratory cancer. This is a statistically significant number ($P<.05$) when compared to the expected respiratory cancer death rate of 6 to 7% for men in this age group. Although these results were considered as "highly suggestive of a carcinogenic risk of ECH," it was also recognized that unresolved difficulties complicated the analysis of results. These problems included the lack of accurate pathological diagnoses in most cases, the absence of quantitative monitoring and exposure data, and the absence of tobacco smoking and alcohol consumption histories. Nevertheless, in conjunction with the results of animal bioassays with ECH (see Section III.B.2.h), this substance must be viewed with increased suspicion.

Dow Chemical (Shellenberger et al., 1979) has reported that among ECH-exposed workers in their Glycerine Department and Epoxy Resins Department, Texas Division, "no association was found between an increased risk of mortality and exposure to epichlorohydrin." However, this conclusion cannot be accepted without reservation, since the cohort described was probably too young (62% under age 40) and too recently exposed (63% with less than 10 years elapsed since onset of exposure) to fully exhibit the effect of chronic ECH exposure on mortality.

2. Effects on Non-Human Mammals

a. Absorption, Distribution, and Excretion

The pharmacokinetics of ECH in mammalian systems has only recently been explored in detail. Weigel and coworkers (1978) have examined the tissue distribution and excretion of ^{14}C-ECH following an oral dose of 10 mg/kg given to male and female Charles River CD rats. Various body tissues were examined at 2, 8, 12, 24, 48, and 72 hours post administration in an attempt to: (1) determine major routes of excretion; (2) observe any sex-related differences in distribution and excretion; and (3) correlate the known target organ effects of ECH with the tissue distribution of the compound. In a separate study, the respiratory excretion of orally administered ^{14}C-ECH was determined by the measurement of $^{14}CO_2$ and unchanged ^{14}C-ECH in expired air at various intervals following exposure.

Interpretation of their results is complicated by the fact that recovery of administered radioactivity was low. Nevertheless, it was apparent that absorption of ^{14}C-ECH was rapid, with peak tissue concentrations being reached at 2 hours in males and 4 hours in females. In general, the tissue with the highest level of radioactivity was the kidney, followed in decreasing order by the liver, pancreas, adrenals, and spleen.

The major route of excretion for ^{14}C-ECH-derived radioactivity was in the urine, accounting for 30-40% of the administered dose within 72 hours. Excretion of $^{14}CO_2$ in expired air accounted for 18-21% of the administered radioactivity (24 hours), whereas fecal excretion accounted for less than 4% of the dose over a 72 hour period. The rapid appearance of large amounts of $^{14}CO_2$ in expired air suggested a rapid and extensive metabolism of ^{14}C-ECH by the rat.

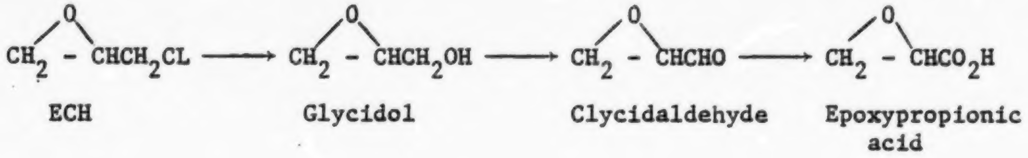
The pharmacokinetics of radiolabelled epichlorohydrin administered to rats by gavage or inhalation have been studied by Dow Chemical (Smith *et al.*, 1979). Rats were administered epichlorohydrin-1,3-^{14}C at levels of 100 or 1 ppm by the two routes indicated. Inhalation studies were conducted for 6 hrs. of exposure. Within 72 hours, 90% of the administered radioactivity had been recovered from the urine (46-54%) and expired air (25-42%). Orally exposed rats showed 9 urinary metabolite peaks, but only eight peaks were observed following inhalation exposure. None of the excreted radioactivity represented unchanged compound. Tissue distribution studies showed similar patterns following either route of exposure, except that nasal turbinates and the stomach showed high levels after inhalation and oral exposure, respectively. Quantitation of relative tissue levels of compound cannot be relied upon, since extensive breakdown of labelled compound to one carbon units occurs, following which redistribution and incorporation can take place.

b. Pharmacology and Metabolism

Only limited data are available concerning the mammalian metabolism of ECH. Nevertheless, it was demonstrated in studies with rats that ECH may be hydrolyzed *in vivo* to yield α-chlorohydrin (Jones *et al.*, 1969). This pathway of metabolism is supported by data indicating that common urinary metabolites are obtained after treatment of rats with either ECH or α-chlorohydrin. The urinary metabolites produced are apparently substituted cysteine derivatives.

Further data to suggest the role of α-chlorohydrin as an intermediate during ECH metabolism are available from studies showing that both compounds produce antifertility effects in male rats (Cooper et al., 1974; see Section III.B.2.f.).

Additional possibilities for intermediates in ECH metabolism were suggested by Van Duuren (1977). The following pathway was postulated:



It is noteworthy that both ECH and glycidaldehyde are suspect as carcinogens (Van Duuren, 1977).

c. Acute Toxicity

Studies with various animal species have established that ECH is highly irritating upon contact and moderately toxic by systemic absorption. The major target organs adversely affected by ECH are the central nervous system, spleen, liver, respiratory tract, and the kidneys (Lawrence et al., 1972). A summary of ECH dose-response information for acute lethality by various routes of administration and in several species is presented in Table 24. Further experimental data are summarized in the following sections of this report.

(1) Acute Inhalation Exposures

In one of the earliest reports on ECH toxicity, white mice were exposed to ECH vapors at 2370, 8300, and 16,600 ppm for 30 or 60 minutes (Freuder and Leake, 1941). A dose-related irritation of the nose and eyes was observed; all of the mice exposed to ECH at 8300 and 16,600 ppm died.

Table 24. Acute Toxicity of Epichlorohydrin (ECH)

Species	Route^{a}	Dose^{b}	Results	Reference
Mouse	oral	238 mg/kg	LD_{50}	NIOSH, 1976a
	oral	0.5 ml/kg	LD_{100}	Freuder and Leake, 1941
	oral	0.23 ml/kg	Not lethal	Freuder and Leake, 1941
	ihl	7,400 ppm x 30 min	LC_{LO}	NIOSH, 1976a
	ihl	2,370 ppm x 1 hr	Not lethal	Freuder and Leake, 1941
	ihl	8,300 ppm x 30 min	LC_{100}	Freuder and Leake, 1941
	ihl	16,600 ppm x 30 min	LC_{100}	Freuder and Leake, 1941
	ihl	71.89 mg/1 x 9.13 min	LT_{50}	Lawrence et al., 1972
	ihl	793 ppm x 2 hr	LC_{50}	Grigorowa et al., 1974
	scu	250 mg/kg	7/10 died	Pallade et al., 1967
	scu	500, 375 mg/kg	LD_{100}	Pallade et al., 1967
	ip	155 mg/kg	LD_{50}	NIOSH, 1976a
	skin	tail dipped in undiluted ECH x 1 hr	6/10 died	Pallade et al., 1967
		tail dipped in undiluted ECH x 20-30 min, 203X	LD_{100}	Pallade et al., 1967

Table 24. Acute Toxicity of Epichlorohydrin (ECH)
(Continued)

Species	Route[a]	Dose[b]	Results	Reference
Rat	oral	90 mg/kg	LD_{50}	NIOSH, 1976a
	oral	260 mg/kg	LD_{50}	Lawrence *et* *al*., 1972
	oral	0.21 ml/kg	LD_{50}	Weil *et* al., 1964
	ihl	360 ppm x 6 hr	LC_{50}	Snyder, 1978
	ihl	250 ppm x 4 hr	LC_{LO}	NIOSH, 1976a
	ihl	635 ppm x 4 hr	LC_{50}	Grigorowa *et* *al*., 1974
	ihl	250 ppm x 8 hr	4/6 died	Weil *et* *al*., 1964
	scu	150 mg/kg	LD_{50}	Pallade *et* *al*., 1967
	scu	125 mg/kg	6% polyuric 79% oliguric 15% normal death rate = 13.4%	Pallade *et* *al*., 1968
	skin	2 ml/kg x 1 hr	18/20 died	Freuder and Leake, 1941
	skin	1 ml/kg x 1 hr	2/10 died	Freuder and Leake, 1941
	skin	0.5 ml/kg x 1 hr	0/10 died	Freuder and Leake, 1941
Rats and mice	ihl	6-7 mg/1	LC_{100}	Kremneva, 1960
	ihl	3 mg/1	LC_{50}	Kremneva, 1960

Table 24. Acute Toxicity of Epichlorohydrin (ECH)
(Continued)

Species	Route[a]	Dose[b]	Results	Reference
Rabbit	skin	1300 mg/kg	LD_{50}	NIOSH, 1976a
	skin	0.64 ml/kg	LD_{50}	Lawrence _et al._, 1972
	skin	1.3 ml/kg	LD_{50}	Weil _et al._, 1964
	skin	0.76 g/kg	LD_{50}	Lawrence _et al._, 1972
Guinea pig	unk (oral?)	280 mg/kg	LD_{50}	Fedyanina, 1968
Cats, dogs	iv	0.08 ml/kg	minimum lethal dose	Krimneva and Tolgskaya, 1961
Mice, rats, rabbits, guinea pigs	ip	0.10-0.14 ml/kg	LD_{50}	Lawrence _et al._, 1972

[a] Abbreviations: ihl, inhalation; scu, subcutaneous injection; ip, intraperitoneal injection; skin, dermal application; iv, intravenous injection

[b] 1 ml ECH $\cong$ 1.18g

Among 10 mice exposed to 2370 ppm ECH for 60 minutes each day, two animals died on day 3, two on day 6, one on day 7, two on day 8, on day 9, and the last two on day 16. Symptoms leading to death included gradual cyanosis, muscular paralysis, and depressed respiration which preceded cardiac arrest.

The acute symptoms of ECH vapor intoxication in rats and mice were further described by Kremneva (1960). She reported central nervous system impairment, characterized initially by locomotor excitability, and followed by nervous depression and breathing difficulty. In addition, a reddening of the skin and subcutaneous hemorrhage were noted.

A more recent report on systemic damage produced by inhalation of ECH was published by Shumskaya and coworkers (1971) in Russia. Rats receiving single four hour exposures to ECH at 1.8 to 91 ppm experienced functional alterations in the kidneys, liver, lungs, and central nervous system. Kidney dysfunction was evidenced by polyuria, proteinuria, reduced urinary chloride levels, and increased urinary excretion of nitrogen-containing substances. Liver and kidney weights were increased, while spleen and lung weights were decreased. Impairment of liver function was indicated by a decreased ability to remove bromosulfophthalein from the blood. Oxygen consumption and body temperature were also reduced by the ECH treatment.

The results of another recent study have shown that the acute six-hour LC_{50} for ECH in male Sprague-Dawley rats is approximately 360 ppm (Snyder, 1978). The range of lethal concentrations was apparently very narrow, suggesting that a critical ceiling may exist for acute inhalation exposures. Pathologic findings on gross autopsy included hemorrhage and edema which presumably resulted from respiratory irritation. In animals still surviving four weeks after the ECH exposure, signs of recovery were evident.

(2) Acute Oral Exposures

Freuder and Leake (1941) first reported the toxic effects of ECH by ingestion. A single dose of 0.5 ml/kg ECH in gum arabic given by stomach tube was lethal to all of a group of 15 animals. No deaths resulted from administration of ECH at 0.23 ml/kg. However, four doses of 0.23 ml/kg each given at daily intervals were lethal to all mice treated. The symptoms of intoxication were the same as previously described for inhalation exposures; death resulted from effects on the central nervous system, primarily the respiratory center.

Kremneva and Tolgskaya (1961) observed the effects of acute oral doses of ECH administered to both rats and mice. At the lowest dose tested, 250 mg/kg, no obvious signs of toxicity were noted during a 14 day observation period. All animals given doses of 325 and 500 mg/kg, however, died within two days. The symptoms observed in both species included decreased locomotor activity, body tremors, muscular incoordination, breathing difficulty, abdominal distention, skin hyperemia, and subcutaneous hemorrhage. Histopathologic examination revealed hepatic vacuolization and fatty degeneration, pulmonary edema and hemorrhage, renal necrosis with epithelial degeneration of the convoluted tubules, and necrotic areas in the gastrointestinal mucosa.

(3) Acute Dermal and Eye Contact

Several investigators established that ECH can produce systemic poisoning from skin absorption. In 1941, Freuder and Leake applied ECH to the bare skin of guinea pigs and rats. On the shaven abdominal area, about 1 cm^2 gauze saturated with ECH was placed and then covered with plastic for one hour. Following the appearance of local discoloration and irritation, symptoms of systemic intoxication occurred. At the 2 ml/kg dose, 18 out of 20 rats died; at 1 ml/kg, 2 out of 10 rats died, while all 10 rats survived the 0.5 ml/kg dose.

A more recent study (Pallade et al., 1967) examined the results of immersing the tails of 20 mice in pure ECH. A one hour exposure was lethal within 3 days to 6 out of 10 mice. Repeated immersions lasting 20-30 minutes each were lethal to all 10 mice by the second or third treatment. Necropsy revealed widespread congestion and edema in addition to brain hemorrhage, as well as severe damage to the epithelium of the renal convoluted tubules. They also found that 15-20 minute immersions of 10 mice's tails in undiluted ECH resulted in the death of seven mice and local damage in survivors leading to the loss of the ends of the tails. Another experiment by Pallade and coworkers (1967) studied the local effects of 0.5 ml of ECH applied for 24 hours to the skin of rabbits. The resulting lesion was described as having a region of necrosis bounded by edema of the superficial skin layers. Peripheral to this area of exposure, erythema and focal points of hemorrhage were observed. A scab covering the area of irritation formed in 2-3 days and lasted as long as 30 days. All rabbits recovered from the treatment. Lesions of lesser severity were observed for applications of 0.1-0.2 ml of ECH.

Several researchers have studied the effects of ECH on the eyes and conjunctivae of test animals. In 1961, Kremneva and Tolgskaya placed a drop of ECH on the conjunctival sac of a rabbit's eye, which resulted in lacrimation, edema and hyperemia of the lid and mucous membrane, corneal clouding, blepharospasm, constriction of the pupil, and reduced eye slit. In 1969, Golubev reported that 0.25 M ECH solution instilled in rabbit's eyes caused no damage to either the cornea or conjunctiva; however, constriction of the pupils occurred on the order of 1-16% of the pretreatment pupil diameter. Lawrence and coworkers (1972) dropped 0.1 ml of ECH dissolved in cottonseed oil into the right eyes of rabbits, leaving the untreated eyes to serve as controls. Corneal injury resulted in 80% of the treated eyes while the remainder suffered irritation to a lesser extent. From these studies, it was concluded that ECH is a strong ocular irritant.

(4) Acute Parenteral Administration

Subcutaneous injection of ECH produces nephrotoxic action in test animals. In 1968, Pallade and coworkers found that single injections of ECH (125 mg/kg) caused polyuria in 6% of the 67 rats treated, and oliguria or anuria in 79%; the remaining 15% exhibited normal urine flow. Seven rats which initially produced little or no urine became polyuric in 2-3 days. Deaths occurred at a rate of 13.4% but was restricted to anuric or oliguric rats. Urinary protein and potassium levels were high immediately after treatment, but returned to normal in 8 days. Sodium concentrations, however, were still low after 8 days (Pallade et al., 1968).

In 1966, Rotaru and Pallade reported that single subcutaneous injections of ECH in rats (150 or 180 mg/kg) caused severe injury to the kidneys, especially to nephrons. Regeneration of the structural components of the kidneys was seen on days 5 and 10 following treatment, but no positive determination could be made from the data available regarding the restoration of function. Injury to the other internal organs was also evident as pulmonary congestion and edema, bronchial catarrh, hemorrhage and congestion of the spleen, congestion and edema of the gastrointestinal tract, and congestion in the brain and adrenals. Changes in the liver and heart were insignificant. Severity of injury appeared to be dose-dependent. Criteria for determining these changes were not available for evaluation.

Two dogs and three cats anesthetized with pentobarbital were injected intravenously with single 0.008 mg/kg doses of ECH. The only effect observed was a temporary drop in blood pressure. The minimum intravenous lethal dose, determined by the same investigators to be 0.08 ml/kg, caused death in 2 hours (Kremneva and Tolgskaya, 1961).

d. Subchronic Toxicity

Repeated oral administration of ECH to both rats and mice has been conducted by various investigators. Four treatments of ECH were sufficient to cause death at a dose level of 0.23 ml/kg (Freuder and Leake, 1941). Fedyanina (1968) found administration of 0.1 mg/ℓ ECH in the water of rats for six months had adverse effects on conditioned reflexes and liver function.

In early studies, Freuder and Leake (1941) severely exposed 10 white mice to 2370 ppm/60 min/day until all had died. All animals exhibited the same sequence of symptoms. Initially eye and nose irritation occurred followed by gradual cyanosis, relaxing of the muscles of the extremities, stiffening of the tail and a slight body tremor. Several hours before death, respiration decreased and ceased before cardiac arrest. In some animals terminal clonic convulsions were observed. Two deaths occurred on the third day, two on the sixth day, one on the seventh day, two on the eighth day, one on the ninth day, and the two final deaths occurred on the sixteenth day.

Gage (1959) exposed groups of Wistar rats by inhalation to varying concentrations of ECH for 6 hours/day, 5 days/week and observed dose-related toxic effects. Rats receiving 11 exposures to ECH at 120 ppm in air began to have difficulty in breathing after the first three hours; this condition persisted throughout the entire series of treatments. The poor condition of the rats became progressively worse and between exposures the rats exhibited symptoms of lethargy. After the fourth exposure the rats had profuse nasal discharge along with considerable reductions in weight. Blood analysis revealed marked leucocytosis due to an increase in polymorphs and monocytes. Urinary protein excretion had more than doubled at the termination of the treatment period. The death of one rat occurred after the eleventh exposure. Necropsy revealed patches of discoloration in the lungs of all rats, two livers exhibited uneven coloration, the kidney cortices of two rats were unusually pale, and intestines were found to contain bile in addition to being distended with gas. Further examinations showed congestion of the lungs, edema, consolidation, and areas of inflammation with possible abscessing. Leucocytic reaction was evident in the kidneys of all rats and in four rats there was atrophy of the peripheral cortical tubules. The degree of functional impairment which accompanied these lesions and their possible reversibility was not determined in this study.

Another group of rats received 18 six-hour exposures to 56 ppm ECH (Gage, 1959). Lethargy and respiratory difficulties were again noted but not until the tenth exposure. A nasal discharge appeared later. Weight losses were recorded during the exposure period but some recovery was made on weekends. Neither urine and blood analysis nor necropsy and histopathological examination revealed any abnormalities. A group of rats receiving 18 exposures at 27 ppm suffered minor nasal irritation but body weights remained constant. Hemorrhage and consolidation was only seen in the lung of one rat. Nineteen exposures to 17 ppm produced no definitive alterations yet the condition of the treated rats did appear to be inferior to normal controls. A final group of rats was exposed 18 times to 9 ppm ECH. No ill effects were noted although two rats suffered pulmonary infections.

Further inhalation studies by Gage (1959) were conducted using New Zealand white rabbits weighing 1.8-2.0 kg. Twenty daily exposures to 35 ppm caused nasal irritation but no alterations in normal weight gain. Two rabbits exposed to 16 ppm (2 exposures) experienced nasal irritation, whereupon the concentration of ECH was then decreased to 9 ppm for 20 days. This treatment produced no adverse effects on the rats, nor were any abnormalities observed in post-mortem examinations.

A comprehensive ECH inhalation study was conducted by Fomin (1966). Male albino rats were exposed in groups of 15 to ECH vapor for 24 hours per day for 98 days at the following dose levels:

a. 20 ± 0.026 mg/m^3 (5.2 ppm ± 0.01); total ECH inhaled = 1722 mg/kg
b. 2 ± 0.007 mg/m^3 (0.5 ppm ± 0.002 ppm); total ECH inhaled = 172 mg/kg
c. 0.2 ± 0.001 mg/m^3 (0.05 ppm ± 0.0003 ppm); total ECH inhaled = 17 mg/kg

Rats exposed to 5.2 ppm ECH vapor exhibited a decrease in total nucleic acid content of the blood to 90.73 mg% (versus 127.07 mg% in the controls) and increase in urinary coproporphyrin to 2.68 μg (versus 1.07 μg in the controls). The health-related significance of these results was not shown. Reduced weight gain and prolonged latent periods in a motor defense reaction test were additional symptoms of ECH exposure cited in this abstract. Necropsy revealed abnormalities of the lungs including emphysema (diagnostic criteria not specified), bronchopneumonia, edematous areas and loosening and swelling of the adventitia of blood vessels. Examination of the kidney found cloudy swellings of the epithelium of the convoluted tubules. Interstitial hemorrhage and venous congestion were noted in the heart. The brain contained severe lesions of neurons in the medulla oblongata, Ammon's herm and the cerebellum. The degree of functional impairment or the reversibility of these lesions was not examined. The groups exposed to 0.5 and 0.05 ppm ECH revealed no morphological abnormalities upon analysis. The low dose (0.05 ppm) group exhibited no blood changes. Analysis of this data is not possible until the full report is available.

A group of ten rats was exposed three hours daily to 0.02-0.06 mg/ℓ (5.2-15.6 ppm) of ECH for 6.5 months. Kremneva and Tolgskaya (1961) recorded no deaths or signs of intoxication attributable to the treatment. Reduced weight gains were found in the treated rats in addition to an increase in the threshold of excitability of the nervous system during months 2-5. Blood pressure was normal in the treated rats and although oxygen consumption increased during the first two months of exposure it decreased during the fifth and sixth months. No abnormalities were found upon analysis of peripheral blood. Examination of the liver and kidney revealed no significant effects. Occasional slight thickening of the alveolar walls and the presence of bronchitis led the authors to conclude that this dose level of ECH was the threshold for production of tissue damage in rats.

Snyder (1978) exposed rats to 100 ppm ECH for 30 days. Although the treated animals had a reduced rate of survival, their rate of weight gain was greater than for controls. Rhinitis and squamous cell metaplasia were evident upon examination of the nasal mucosa. Chronic exposure to 30 ppm ECH for more than 734 days or 10 ppm ECH for more than 670 days resulted in increased survival of treated groups versus controls. Those rats exposed to 30 ppm exhibited significant weight losses, however. Further details of this study are reported in Section III. B. 2. h.

A Dow Chemical Study on the subchronic toxicity resulting from ECH inhalation in rats and mice has been carried out by Quast et al. (1979). Two species of rats and one of mice (both sexes) were exposed to ECH vapor at concentrations of 5-50 ppm for 6 hours/day, 5 days/week for a total of 65 exposures. Pathological changes were noted primarily at the two highest exposure levels, 25 and 50 ppm. All species and sexes showed inflammatory and degenerative changes in the nasal turbinates; male Sprague-Dawley rats showed the most severe changes. These included rhinitis, focal erosions, hyperplasia, and metaplasia with a squamous appearance. Moderate and severe focal tubular nephrosis was observed in the high dose rats. Gross pathological changes in the livers of high exposure male rats were seen in half the animals. This included pale discoloration and accent ratios of the lobular pattern. However, histopathology did not reveal significant microscopic changes. Several male rats from the 50 ppm group showed altered epididymal contents which included amorphous eosinophilic staining material and increased numbers of nucleated cells. The sperm count in these animals was normal. Weight loss in the 50 ppm exposure groups was slight. The role of secondary effects produced by stress at the highest ECH exposure is difficult to evaluate, but is probably not a major factor.

A follow-up on this study by the same investigators (Quast et al., 1979) utilized continuous 7 hour exposures to higher ECH vapor levels for 12 consecutive days. At the exposure level of 100 ppm, rats and mice showed symptoms of decreased body weight, nasal irritation, and increased kidney weights (rats). The changes in the nasal turbinates observed were similar to those noted in the previous study except that they were more severe. Slight degenerative changes were noted in the kidneys of the rats, and slight non-degenerative changes were seen in the rats and mice. Changes in epididymal contents were the same as those observed after the longer 50 ppm exposure. No evidence of cystic or degenerative changes in the epididymides was noted in this study.

Grigorowa and coworkers (1974) studied the effect of environmental stress on the response of 60 male albino rats exposed by inhalation to 0.6 or 0.06 mg/liter (15.8-158 ppm) ECH for four hours per day over an eight-day period. One half of each exposure group was subjected to a temperature of 35°C and relative humidity of 35-50% for 45 minutes after each exposure to ECH. Exposure to the higher dose of ECH reduced body weight by 9%; exposure to ECH and stress had the same effect. Examination of rats throughout the study revealed a modification of the toxic effects of ECH by the addition of heat stress. Those rats subjected to heat stress suffered less severe variations in liver and thyroid follicles but the effects on the adrenal medulla were increased. Leukocyte accumulation around blood vessels was noted in the thyroids of five rats. Compared to controls, the treated animals exhibited increased relative weights of lungs, liver, kidneys and adrenals. Urinalysis revealed a decrease in volume and protein concentration. Serum lactate dehydrogenase activities increased while serum sodium, potassium and leucine aminopeptidase showed variable changes. The authors found an increase in blood catalase activity to be the main effect of heat stress and noted that these effects were less severe at the lower dose of ECH.

Rats exposed to 32 ppm ECH for a period of 91 days, 7 hours per day, 5 days per week suffered reduced weight gains. Exposure to 16 ppm on the same schedule produced an increase in kidney size and small amounts of coproporphyrins in the urine (ACGIH, 1974).

Fomin (1968) in a later study exposed mice to 20 mg/m^3 (5.3 ppm) of ECH producing weight loss, deterioration of conditioned reflexes and unspecified morphological changes of some organs and the central nervous system. A smaller dose, 2 mg/m^3 (0.5 ppm), increased the white blood cell counts in mice.

Lawrence and coworkers (1972) undertook a comprehensive study of the cumulative and subchronic parenteral toxicity of ECH in rats. Groups of 12 male Sprague-Dawley rats were employed. The controls received daily injections of cottonseed oil for 30 consecutive days while another group received 0.00955 ml/kg (0.1 acute LD_{50}) of epichlorohydrin daily, and a final group 0.01910 ml/kg ECH (0.2 acute LD_{50}). No deaths occurred during the 30 treatment days in any group. However, weight gains in the treated rats were significantly less than those recorded for the controls. These differences were significant after 15, 20, and 30 days at the high dose and after 20 days for the low dose. ECH had no apparent effect on hepatic function as evidenced by the sodium sulfobromophthalein disappearance test. There was a significant increase in hemoglobin in those rats exposed to the low dose of ECH, but a decrease at the high dose. There was a significant increase in neutrophilic metamyelocytes (metas) at the high dose as well. The organ to body weight ratios did not differ from the controls except for a statistically significant dose-related increase in the kidney to body weight ratio. Lesions of the lungs including bronchitis, peribronchitis, interstitial pneumonia, and emphysema were observed in all groups but their severity and incidence were slightly greater in the ECH-treated rats.

Another subchronic study (Lawrence et al., 1972) was conducted using 4 groups of male Sprague-Dawley rats. Each group received intraperitoneal injections of ECH 3 days/week for 12 weeks. The control group was given cottonseed oil and each of the other groups received injections of 0.0095 ml/kg, 0.0190 ml/kg, 0.04774 ml/kg of ECH corresponding to 0.1, 0.2, and 0.5 of the acute LD_{50} As a result of the treatment, animals in the two higher dose groups consumed less food when expressed on a per body weight basis (significant only for the first week at the highest dose and the twelfth week at the middle dose). Throughout the study, the highest dose group exhibited significantly reduced weight gain, but by the end of the 12-week study none of the three groups differed significantly from the controls. Hematologic parameters showed a significant dose-related decrease in hemoglobin in addition to lower hematocrit values and erythrocyte counts in all treated groups (significant for the middle dose only), and 72% higher mean corpuscular volume at the low dose. Other suggested trends, although not statistically significant, were a general increase in platelets; an altered total leukocyte count, the low dose being less than the controls and the high dose greater; a dose-related increase in percent of neutrophils (significant at the high dose); increase in percent of eosinophils in all treated groups (significant for the high and low doses only); and a decrease in percent of lymphocytes (significant for the two highest doses). The organ to body weight ratios differed significantly from the controls at the high doses only. The brain to body weight ratio was 27% less, but the organ to body weight ratio for the heart, kidneys, liver and spleen were 29.1 to 38.1% greater than controls, thus ruling out simple growth retardation as a cause.

e. Sensitization

Two studies have evaluated the sensitization of guinea pigs with epichlorohydrin (Weil _et_ _al_., 1963; Lawrence _et_ _al_., 1972). Lawrence _et_ _al_. (1972) found no sensitization after application of 0.01% epichlorohydrin in cottonseed oil by the method of Magnnsson and Klingman. This test involved only five animals. Weil _et_ _al_. (1963) injected 18 guinea pigs eight times with 0.1 ml of diluted material (concentration not specified) and challenged these animals 3 weeks later. No positive reactions were observed.

f. Reproductive and Teratogenic Effects

Dow Chemical has in progress a study of the teratogenic and embryotoxic effects in rats and rabbits of ECH inhalation (John _et_ _al_., 1979). The animals were exposed to 2.5 or 25 ppm ECH for 7 hrs/day during days 6-15 or days 6-18 of gestation for rats and rabbits, respectively. Rats exposed to 25 ppm ECH showed maternal weight loss and an increased resorption rate. This increase was not significant when compared to the historical rate of resorptions in these animals. Similarly, rabbits exposed to 2.5 ppm ECH showed an increased resorption rate which was not significant compared to historical controls. Examinations of external and soft tissue alterations in both groups showed no teratogenic effects. Examination of fetal heads in rats and fetal skeletal alterations in both groups has not been completed.

The antifertility properties of ECH have been investigated by several researchers. Hahn (1970) administered 15 mg/kg day of ECH orally to male Sprague-Dawley rats (240-260 g) for 12 days. The fertility of the males was determined by placing two pre-estrous females in the cage of each male overnight. After seven days, the number of uterine implantations was counted as an index of fertility. One week of treatment left all males sterile. Within one week after treatment, however, the sterility was reversed. A histopathological examination on the twelfth day showed no abnormalities of the testis, epididymis, or prostate or seminal vesicles. Neither libido nor ejaculation were adversely affected.

Further studies were conducted by Cooper and coworkers (1974). ECH was administered orally to adult male Wistar rats (280-320 g) in a suspension of arachis oil at several dose levels. The average weekly litter size in females mated to the ECH-treated males was recorded and the data are presented in Table 25.

Table 25. Effect of Epichlorohydrin on Fertility in Male Rats[a]

		Average weekly litter size in mated females									
Dose Level	Weeks:	1	2	3	4	5	6	7	8	9	10
5 x 20 mg/kg		0	0	9	11	11					
5 x 50 mg/kg		0	0	0	0	0	0	0	0	0	0
1 x 100 mg/kg		0	4	3	4	4	2	2	4	2	3

[a] Cooper _et_ _al_., 1974.

A single dose, 1 x 100 mg/kg, did not render the males infertile as did several small doses, 5 x 50 mg/kg. The effect of several smaller doses (5 x 50 mg/kg) of ECH was found to be similar to a single larger dose (1 x 100 mg/kg) of α-chlorohydrin, a presumed ECH metabolite. The single larger dose of ECH reduced fertility but did not cause any serious histological aberrations after eight weeks of observation, except for small spermatocoeles in the ductuli efferentes; this is in contrast to a single 100 mg/kg dose of α-chlorohydrin, which did induce sterility. Large retention cysts were present in the ductuli efferentes and the proximal caput became sterile 12 weeks after exposure in four of the five test animals.

The suggested mode of antifertility action for ECH is the *in vivo* hydrolysis of the epoxide ring to yield α-chlorohydrin (Hahn, 1970; Cooper *et al*., 1974; Jones, *et al*., 1969). Jones *et al*. (1969) conducted *in vitro* experiments with α-chlorohydrin and found it to be an effective antifertility agent. Further experiments in which ECH or α-chlorohydrin were administered to Wistar rats, showed that both caused sterility and 2,3-dihydroxypropyl-S-cysteine was excreted in the urine of all animals. The presence of a common urinary metabolite indicates that ECH may be hydrolyzed *in vivo* to α-chlorohydrin and then further metabolized to an intermediate which affects spermatogenesis (see Section III.B.2.b.). Mashford and Jones (1978) have suggested that the final metabolite, 3-chloro-1,2-propanediol phosphate, is responsible for this effect on spermatogenesis.

g. Mutagenicity

(1) Epichlorohydrin

Without prior metabolism (i.e., metabolic activation) ECH has been shown to cause reverse mutations in several microorganisms (Table 26). *Salmonella typhimurium* has been the organism most commonly used in these studies (i.e., Ames assay) and information on the dose-response of ECH

Table 26. Reverse Mutations Induced by Epichlorohydrin
Without Metabolic Activation

Species	Concentration	Response	Reference
Escherichia coli	0.017 *M*	Increase of 30 mutations/ mole/minute over background.	Strauss and Okubo, 1960
	1.27 *M*	A 20-fold increase in mutations over control.	Mukai and Hawryluk, 1973
Klebsiella pneumoniae	0.00637 *M*	A 45.4-fold increase in mutations over control.	Voogd, 1973
Neurospora crassa	0.15 *M*	Increase of 20 mutations/ mole/minute over background at optional conditions.	Kølmark and Giles, 1955
Salmonella typhimurium	1.27 *M*	A 20-fold increase in revertants over control.	Mukai and Hawryluk, 1973
	0.001 *M*	An unspecified increase in the number of mutations over control values.	Voogd, 1973
	0.00030-0.005 *M*	A significant dose-related increase in the number of revertant colonies per plate.	Elmore *et al.*, 1976
	0.001-0.108 *M*	A increase up to 5.3 x 10^6 relative mutation frequency over control values (see text).	Sram *et al.*, 1976 a and b

exposure to mutagenesis has been provided by Elmore and coworkers (1976) and Sram and coworkers (1976a,b). In *Salmonella typhimurium* strain TA100 -- used to detect base-pair substitutions -- ECH caused a dose-related increase in the number of revertant colonies per plate after a 48 hour incubation period. Plotted on log-log paper, this increase was linear over a concentration range of about 30 micromolar (which resulted in about 20 revertant colonies per plate) to about 500 micromolar (which resulted in about 800 revertant colonies per plate). In the same study, ECH did not inhibit the growth of a repair deficient strain of *Bacillus subtilis* (Elmore *et al*., 1976). Sram and coworkers (1976a&b) used two strains of *Salmonella typhimurium*, TA100 and G-46, and measured the dose-response relationship after 60 minute exposure periods to various concentrations of ECH. The index of mutagenicity was taken as the number of revertants in the experimental group divided by the number of revertants in untreated controls. In strain G-46, ECH concentrations of 0.108 *M* and 0.054 *M* caused 5.3×10^6 and 280-fold increase, respectively, in the mutation index as well as marked decreases in cell survival. In strain TA100, 0.054 *M* ECH caused a 220-fold increase in the mutation index. Similarly, in a host-mediated assay using ICR female mice given single intramuscular or subcutaneous injections of 50 mg/kg or 100 mg/kg, increased reverse mutation frequencies (up to 5-fold) were seen in *Salmonella typhimurium* strains G46, TA100, and TA1950.

In the dominant lethal assay, ECH has yielded negative results. This assay system, however, is not highly sensitive to mutagens. Epstein and coworkers (1972) administered ECH i.p. to male ICR/Ha Swiss mice as a single dose of 150 mg/kg. Over an eight week mating period, early fetal deaths and preimplantation losses were within control limits. Similarly, Sram and coworkers (1976a) administered the following doses of ECH to male ICR mice:

single i.p. injections: 5, 10, and 20 mg/kg
single oral doses: 20 and 40 mg/kg
multiple i.p. injections: 1 mg/kg x 5, 4 mg/kg x 5
multiple oral doses: 4 mg/kg x 5, 16 mg/kg x 5

Over an eight week mating period, early fetal deaths were not noted.

Although negative in the dominant lethal assay, ECH has been shown to induce genetic damage in higher organisms. Rapoport (1948) reported that unspecified levels of ECH caused 4 mutations in a total of 526 chromosomes in *Drosophila melanogaster*. No mutations were seen in 887 chromosomes from a control group. More recently, Sram and coworkers (1976a) have found chromosomal abnormalities -- primarily chromosome breaks -- in the bone marrow of ECH-treated mice. These results are summarized in Tables 27 and 28.

These data are difficult to interpret since the authors do not indicate what the distribution of breaks within the test population is, or the size of this test population.

Dow Chemical has conducted a study on the cytogenetic effects of ECH treatment in rats (Dabney *et al*., 1979). Test animals were exposed to ECH at levels of 5-50 ppm for 6 hours/day, 5 days/week for a total of 20 exposures. Bone marrow cells, scored for chromosome breaks, showed a trend toward increased chromosomal aberrations at the 25 and 50 ppm exposure levels. However, when the frequency of breaks was analyzed, less than one abnormal cell per animal was found. The investigators have recommended a repeat of this study scoring more cells per bone marrow sample and using a

Table 27. ECH Induced Changes in Mouse Bone Marrow by Intraperitoneal Application (Sram *et al*., 1976a)

Dose mg/kg	h	Total number of cells	Abnormal cells (%)	Breaks % cells	B/C	Gaps % cells	G/C
		Single application					
1	24	250	5.2	2.8	0.003	3.2	0.040
3	24	250	8.4	6.0	0.084	3.2	0.040
5	24	250	10.8	10.0	0.112	3.2	0.032
10	24	250	21.6	16.0	0.360	7.2	0.095
20	24	250	28.4	27.2	0.488	3.2	0.040
50	24	250	27.6	20.4	0.360	9.2	0.124
50	6	250	32.8	30.0	0.560	12.8	0.204
50	48	250	22.0	23.6	0.392	6.4	0.088
		Repeated doses (interval between doses 24 h)					
5 x 10	6	250	35.2	20.8	0.350	12.8	0.170
		Repeated doses (5 doses per 7 days)					
5 x 5	6	250	38.0	37.2	0.692	7.2	0.072
5 x 10	6	250	36.0	33.6	0.600	9.2	0.124
5 x 20	6	250	80.4	78.8	2.176	5.2	0.080
Control DMSO		500	4.0	0.6	0.006	3.8	0.038

B/C, G/C - Breaks, gaps per cell

Table 28. ECH Induced Changes in Mouse Bone Marrow by Peroral Application (Sram _et al_., 1976a)

Dose mg/kg	h	Total number of cells	Abnormal cells (%)	Breaks % cells	B/C	Gaps % cells	G/C
		Single application					
5	24	250	6.0	4.8	0.064	2.0	0.020
20	24	250	24.0	23.2	0.372	3.2	0.036
40	24	250	22.4	17.6	0.288	9.2	0.132
100	24	250	29.5	25.2	0.372	12.4	0.176
100	6	250	30.0	23.2	0.350	12.8	0.175
100	48	250	34.0	32.0	0.648	4.4	0.052
		Repeated doses (interval between doses 24 h)					
5 x 20	6	250	30.4	26.0	0.648	12.8	0.185
		Repeated doses (5 doses per 7 days)					
5 x 20	6	250	36.0	29.2	0.460	12.8	0.184
Control DMSO		500	4.0	0.6	0.006	3.8	0.038

B/C, G/C - Breaks, gaps per cell

higher range of ECH exposure. According to their calculations, this regimen could have achieved total ECH exposure levels comparable to those used by Sram *et al*. (1976a); however, their results indicate a lower frequency of aberrations than this earlier study reported.

(2) Epibromohydrin

Kølmark and Giles (1955) evaluated the mutagenicity of both ECH and EBH to *Neurospora crassa*. Under optimal conditions i.e., the combinations of concentration and exposure period yielding the highest mutation incidence -- EBH induced only 3 mutations/mole/minute of exposure. Thus, in this test system, EBH is markedly less mutagenic than ECH, which induced 20 mutations/mole/minute (see Table 26).

h. Carcinogenicity

While ECH appears to have only limited tumorigenic potential when applied dermally, positive carcinogenic effects have been observed when the compound is administered by injection or inhalation exposures.

Dermal applications of ECH, in the absence of a promoting agent, have resulted in no evidence of tumor development in mice. Weil and coworkers (1964) painted the clipped backs of 90-day old C3H mice (sex not specified) with a "brushful" of undiluted ECH three times weekly for 25 months. All mice were observed until death. Of the 40 mice in the experimental group, only one survived after 24 months of exposure. No skin tumors were noted in any of the exposed animals. No apparent attempt was made to identify tumors in other tissues. In a similar study, Van Duuren and coworkers (1974) applied 2.0 mg of ECH in 0.1 ml of acetone to the shaved backs of 6-8 weeks old female ICR/Ha Swiss mice thrice weekly for 83 weeks. All animals were completely autopsied, except for the cranial region. Papillomas were defined as skin lesions which reached 1 mm^3 in size and persisted for 30 days or more. Of the 50 mice exposed to ECH in acetone, none developed papillomas or carcinomas.

Van Duuren and coworkers (1974) also conducted a comparison study to evaluate the ability of ECH to initiate the tumorigenic process. In this study, a single application of 2.0 mg ECH was made to shaved backs of 30 mice (same age, sex, and strain as above). Two weeks after this application, 2.5 micrograms phorbol myristate acetate (PMA) was applied thrice weekly for 53 weeks to the same site. In this group, 9 mice developed papillomas, the first tumor appearing 92 days after the initiation of PMA treatment, and one organism developed a carcinoma. Three papillomas developed in 30 mice exposed to PMA alone and no tumors developed in 30 mice exposed to acetone alone or in 100 untreated control organisms. Based on these results, Van Duuren and coworkers concluded that ECH is not a mouse-skin whole carcinogen but does have a low order tumor initiation activity.

Injections of ECH have been shown to cause an increased incidence of malignant tumors in mice. As part of the same study cited above, Van Duuren and coworkers (1974) administered 1.0 mg of ECH in 0.05 ml tricaprylin by subcutaneous injection in the left flank of 50 mice. The material was injected once weekly for 83 weeks. Six of the exposed animals developed sarcomas and one developed an adenocarcinoma at the injection site. This tumor incidence was significantly ($p<0.05$) greater than that seen in vehicle and untreated control organisms. On the same dose schedule, 30 mice given intraperitoneal injections of ECH in tricaprylin for 64 weeks developed no local sarcomas but 11 mice did develop papillary lung tumors. However, the incidence of papillary lung tumors was similar to that seen in vehicle controls (10/30) and untreated controls (29/100).

Kotin and Falk (1963) administered single 5 micromole -- about 0.5 mg -- doses of ECH by subcutaneous injection to 30 C3H strain mice. Over a two year observation period, the following tumors were noted: four malignant lymphomas, two lung adenomas, one hepatoma, and one skin papilloma. The incidence of hepatomas and lung adenomas was comparable to that seen in control organisms. However, the incidence of malignant lymphomas was twice that seen in control organisms, and no skin papillomas were seen in control organisms.

Inhalation studies on the carcinogenicity of ECH are currently being conducted at the New York University Medical Center, Institute of Environmental Medicine. A summary of these studies have been forwarded to the EPA, OSHA, NIOSH, and other interested parties by Dr. Norton Nelson (Nelson, 1977) and a more recent update has appeared (Nelson, 1978). In two parallel studies, groups of 40 and 100 Sprague-Dawley rats were exposed to 100 ppm ($\sim$380 mg/m^3 ECH for 6 hours per day for 30 days. Out of the 140 exposed rats, 13 have died with squamous cell carcinomas of the nasal cavity. In addition, rhinitis and squamous metaplasia have been noted in the living epithelium of the nasal cavity. No such effects were seen in control organisms. Nelson (1977) has commented on the rarity of squamous cell carcinomas of the nose in rats. This is the same type of tumor caused by bis(chloromethyl)ether (Leong et al., 1975). In further studies conducted by the same investigators, Sprague-Dawley rats are receiving chronic lifetime exposures to ECH vapors at a level of 30 ppm, 6 hours per day, 5 days per week. Out of 100 animals, 2 have thus far (∿ 2 yrs.) developed tumors. One has developed a nasal squamous cell carcinoma and the other showed a papilloma of the larynx. None of the animals exposed to 10 ppm epichlorohydrin has shown this type of tumor development to date. The results have led the investigators to conclude that, "our findings strongly suggest a potential risk to workers from exposure to ECH" (Nelson, 1978).

3. Effects on Other Vertebrates

No data are available.

4. Effects on Invertebrates

ECH is an effective organic fumigaut against larval wireworms. The LD_{50} for Limonius canus and Limonius californicus was determined in the laboratory in a silt loam soil and was found to be 67.2 ppm (Lehman, 1942).

5. Effects on Plants

The cytogenetic effects of ECH were studied by Akhund-Zade and Kasumova (1974). Pea and chick-pea seeds were exposed to ECH at a concentration of 0.028 - .01% for 6 hours. Delayed disruption of chromosomal meiosis and accelerated aging of both the pea and chick-pea plants were noted.

ECH is known to greatly accelerate abscission and increase the percentage abscission in seedlings. Hall and Liverman (1956) treated the distal ends of the petioles of Gossypium hirsutum with a 1% lanolin paste of epichlorohydrin. Following the chemical treatment, the seedlings were exposed to various light regimes. Those seedlings exposed to far-red light showed greater increases in abscission than those maintained in darkness, room-light, or red light.

6. Effect on Microorganisms

Bringmann (1975) conducted a study to determine the effect of ECH on the proliferation of Microcystis aeurginosa. Varying concentrations of ECH (period dilution) were added to test cultures to find the lowest concentration at which inhibition of cell numbers occurred. The cell number was measured by turbidity and the resulting degree of transmission of monochromatic light (mercury light-5780nm). If the mean transmission of light after the test was 1% greater than the mean value using non-toxic material, the substance is considered to be damaging. The concentration at which the first signs of inhibition were noted for ECH was found to be 6 ppm (ion concentration).

IV. Regulations and Standards

A. Current Regulations

Epichlorohydrin has been designated as a Class 1C flammable liquid and Class B poison; necessary labeling is specified in 49CFR. The following label has been proposed by NIOSH 1976b):

EPICHLOROHYDRIN
POISON! FLAMMABLE!
SKIN CONTACT CAUSES DELAYED BURNS
Avoid contact with eyes, skin, and clothing.
Avoid breathing vapor.
Use only with adequate ventilation.
Keep away from heat and open flame.
Keep container closed.
Do not take internally.

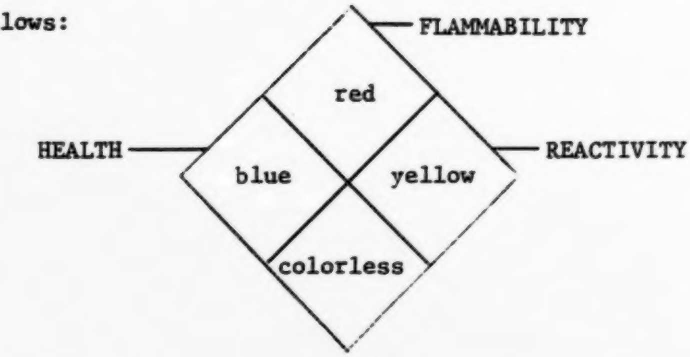
First Aid: In case of skin contact, immediately remove all contaminated clothing, including footwear, wash skin with plenty of water for at least 15 minutes and call a physician. In case of eye contact, flush eyes with water for 15 minutes and call a physician.

The following sign should be posted where there is danger of occupational exposure (NIOSH, 1976b):

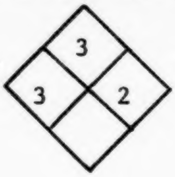
EPICHLOROHYDRIN
POISON! FLAMMABLE!
SKIN CONTACT CAUSES DELAYED BURNS
VAPOR IRRITATING TO EYES
HARMFUL IF SWALLOWED OR INHALED

1. NFPA Hazard Identification Code

The hazard identification system recommended in the National Fire Protection Guide provides basic emergency information on health, flammability and reactivity. The NFPA (1975) symbol includes color and numerical codes as follows:



Each diamond is assigned a number from 0 (no special hazard) to 4 (severe hazard or danger). The NFPA symbol for ECH is:



B. Food Tolerances

1. Food

The use of ECH as a direct and indirect food additive is restricted according to the Code of Federal Regulations. ECH crosslinked with ammonia may be safely used as an ion-exchange resin in the treatment of food and potable water (21 CFR 173.25). ECH may also be employed as a crosslink in molecular sieve resins used in processing foods (21 CFR 173.40). Food starch may be etherified by treatment with ECH (not to exceed 0.3%) alone or in conjunction with propylene oxide, acetic anhydride or succinic anhydride (21 CFR 172.892).

Various resins of ECH can be used in the manufacture of paper and paperboard which will be in contact with dry aqueous and fatty foods. Restrictions pertaining to this use are set forth in paragraphs 176.170 and 176.180 of 21 CFR. 4,4'-Isopropylidenediphenol-epichlorohydrin resins (minimum molecular weight 10,000) and 4,4'-isopropylidenediphenol-epichlorohydrin thermosetting epoxy resins may be used as articles or components of articles intended for food related uses (21 CFR 177.1440, 177.2280).

2. Pesticides

ECH is exempt from tolerance levels when used with good agricultural practice as an inert ingredient (stabilizer) in pesticide formulations.

It must not comprise more than 2% of the pesticide formulation and must be applied before the crop emerges from the soil or in the case of soil fumigants before and after the crop emerges.

3. Standard for Human Exposure

The American Conference of Governmental Industrial Hygienists (1974, 1977) has established a threshold limit value of 5 ppm for ECH in air. This criterion is intended to prevent irritation as well as acute and chronic systemic toxicity, but is probably not low enough to prevent flareups when a previous high sensitizing exposure has occurred.

A time-weighted air concentration of 0.5 ppm for a 10 hour workday, 40 hour week, with a ceiling concentration of 5 ppm has been recommended by the National Institute for Occupational Safety and Health (NIOSH, 1976b). This exposure level was designed to prevent the acute and chronic effects of ECH exposure, skin irritation, and is measurable as well as attainable by techniques available to industry and government agencies. The OSHA standard for ECH is presently 5 ppm. The maximum permissable concentration for the U.S.S.R. (1967) is 0.25 ppm (ACGIH, 1974).

C. Current Handling Practices

1. Special Handling in Use

Protective clothing and equipment must be used to prevent exposure of workers to ECH. The type of respiratory protection required is dependent upon the maximum exposure concentration (NIOSH, 1976b). For concentrations of 25 ppm or less, a gas mask with an organic vapor canister is sufficient, or a type C supplied-air respirator may be used. During emergency conditions, self-contained breathing apparatus with a full facepiece or an air-supplied respirator with an auxiliary air supply must be worn. For further information on respirator types at various concentrations consult the NIOSH Criteria Document on Epichlorohydrin.

NIOSH-approved splash proof goggles as well as gloves and other protective body coverings should be worn as needed to prevent contact with eyes and skin (Shell, 1976). ECH is capable of penetrating neoprene, rubber, and leather. Their use in protective clothing is unsuitable; instead polyethylene, polypropylene, polyvinyl chloride, and other low permeability materials should be used (NIOSH, 1976b). Both local and general mechanical ventilation are highly recommended for work areas (Shell, 1976).

Decomposition of ECH results in the production of hydrogen chloride, phosgene, and carbon monoxide. Conditions to avoid include temperatures greater than 600°F and contact with acids; bases; amines; NH_3; Na, Zn, Al, Mg and their alloys; and Fe, Al and Zn halides. Contact with these substances may cause hazardous polymerization (Shell, 1976).

2. Storage and Transport

ECH should be stored in tightly closed containers in a cool, well ventilated area away from the incompatible materials listed above (Shell, 1976). Discoloration and turbidity have resulted when stored in contact with copper and lead (Shell, 1969).

Electrical equipment in surrounding areas should be compatible with Article 501 of the National Electrical Code for Class I hazardous locations (NFPA, 1975).

3. Accident Procedures

a. First Aid

Medical attention should be sought immediately upon accidental exposure to ECH. The victim should be removed to fresh air and if necessary artificial respiration should be administered.

Clothing and shoes which have been contaminated must be removed and later destroyed. If contact with the skin or eyes has occurred, wash with water for at least 15 minutes. If accidentally ingested, induce vomiting except when victim is unconscious (Shell, 1976).

b. Spill or Leak Procedures

In case of a spill or leak, all ignition sources and unprotected personnel should be removed. A small spill can be absorbed with an inert material whereas large quantities should be collected into containers or vacuum trucks. Label ECH POISON, KEEP OUT OF ALL PUBLIC WATER SUPPLIES AND SEWERS. The proper authorities should be notified if exposure to the general public or environment may occur as a result of a spill or leak (Shell, 1976).

ECH may be disposed of by controlled burning in equipment capable of handling hydrogen chloride fumes and under approved EPA conditions.

The Environmental Protection Agency has proposed the addition of ECH and 27 other chemicals to the 271 chemicals already designated as hazardous and governed by EPA's hazardous spill rules (Anon. 1978a).

V. Exposure and Effects Potential

A. Human Exposure

Because it has not been produced in significant quantities, there does not appear to be any potential for human exposure to EBH. Human exposure to ECH can occur to worker populations, general populations near manufacturing and use plants, and possibly to consumer populations who use epoxy resin preparations. Because of ECH's reactivity in water (half-life of 4 to 8 days) and air (exact rates unknown), it appears unlikely that ECH will be a widespread environmental contaminant. Exposure to worker populations should be below the OSHA standard of 5 ppm and it is likely that general populations near plants or consumer populations will be exposed to concentrations which are considerably less, except where spills or accidents occur. Such a spill has occurred at Point Pleasant, W. V., where significant amounts of ECH were subsequently found in water (Rosencrance, 1978). The general lack of monitoring information in the United States precludes more exact estimates of exposure to human populations. A group of 93 epoxy resin workers (Anon. 1978a) were apparently exposed to concentrations of less than 5 ppm. Several Russian studies have reported worker populations exposed to concentrations of approximately 5 ppm (Kucerova et al., 1977 - 0.13 to 1.3 ppm; Pet'ko et al., 1966 - 4.9 to 5.5 ppm; and Kovalenko and Bokav, 1975 - 0.06 to 0.8 ppm). In another Russian study, Fomin (1966) detected 0.1 to 3 ppm ECH in the air within 100 to 200 meters of a factory; also 5 of 29 air samples at 400 meters from the factory exceeded 0.05 ppm. Pinchuk et al. (1969) detected ECH in the atmosphere of a building whose construction employed extensive use of plastic water-rails. Whether this is representative of the situation in the U.S. is unknown. However, based on air emission estimates of Gruber (1976), we have estimated an annual release of 600,000 lbs of ECH from the three known manufacturing plants. Amounts of ECH in water effluents appear to be very small based upon reviews by Gruber (1976) and Pervier et al. (1974) but little monitoring data is available.

The effects on humans from chronic inhalation of ppm quantities or less of ECH is not conclusively known. However, the possible carcinogenic threat to man by ECH must be considered in deriving public health risk assessments. Current exposure standards (i.e. OSHA) do not take into consideration the recent data implicating ECH as a carcinogen/mutagen in humans and experimental mammals.

The absence of quantitative exposure data in the single epidemiologic study which associates ECH exposure with excess cancers prevents the formulation of dose-response relationships. Nevertheless, many cancer assessment models are based on a non-threshold strategy, and thus predict that a real risk occurs at all dose levels. Therefore extrapolation from presently available animal bioassay data may indicate a carcinogenic threat to man from ECH at any concentration in the environment.

B. Environmental Effects

No ambient monitoring data on ECH or ecological effects information is available from which reasonable conclusions can be reached on the potential for exposure to and effects on the ecosystem. Most emissions appear to be atmospheric and the stability of ECH in air is unknown. No major water effluents are suggested except for the spill in Point Pleasant, W. V. However, if there are major water releases, ECH is stable enough (half-life 4 to 8 days) to travel significant distances. Surface water (to a 1 meter depth) containing

ECH could show evaporative losses; the half life of ECH at 20° and this depth is ∿2 days (p. 76). No significant effects on fish, invertebrates, plants, etc., have ever been studied.

VI. Technical Summary

In 1977 the annual production of epichlorohydrin (ECH) was roughly 400 million lbs. and production capacity was 640 million lbs. (SRI, 1977). The chemical is manufactured by two companies (Dow and Shell) at three locations (Freeport and Deer Park, Texas, and Norco, Louisiana). ECH is primarily consumed as a chemical intermediate in the production of glycerin and epoxy resins. On a percentage basis, the consumption of ECH in 1973 was as follows: glycerin, 46% (produced from crude, unrefined ECH); epoxy resin, 39%; exports, 4%; elastomers, 2%; and other products, 9% (Oosterhof, 1975). Since then the quantity used for glycerin has remained approximately the same while the epoxy resin market has increased substantially (Chemical Marketing Reporter, 1978b). Epibromohydrin (EBH) was used as an intermediate in the manufacture of a nematocide some years ago by the Great Lakes Chemical Corporation. The last batch (roughly 20,000 lbs.) was made in 1975 and, therefore, EBH is no longer a significant commercial chemical, although Great Lakes has retained the ability to manufacture more in the future.

ECH is produced by the "allyl chloride" route which consists of (1) reaction of propane with free-radical chlorine to form allyl chloride, (2) reaction of allyl chloride with hypochlorous acid to yield a mixture of dichlorohydrins, and (3) reaction of the dichlorohydrins with calcium on sodium hydroxide to form the epoxide ring and yield ECH.

Two detailed studies of effluents from an ECH production plant and from a glycerin plant using ECH as a feedstock have been conducted. Based upon a study of an ECH plant by Gruber (1976), the following annual amounts of pollutants from total ECH production are estimated (thousands of pounds): Atmospheric venting-ECH - 600, allyl chloride - 800; trichloropropane - 200, chlorine - 0.2, hydrogen chloride - 0.2; Water from separation - dichlorohydrin - 4000; Heavy ends from fractionator requiring disposal - ECH-424, chloroethers - 2960; dichlorohydrin - 2280; and trichloropropane - 14,840. Gruber (1976) reported that the heavy ends from the fractionator are stored for eventual thermal destruction by incineration. The study by Pervier et al. (1974) only examined atmospheric emissions and their estimates were in basic agreement with the work of Gruber (1976).

Dow (1979) and Shell (1979) have commented that the estimates of Gruber (1976) and Pervier et al. (1974) are much too high as they do not reflect current technology. Shell (1979) estimates that the Gruber (1976) data is on the order of 300 times too high with respect to ECH emissions.

On January 23, 1978, a major spill of ECH occurred in Point Pleasant, West Virginia, when a tank car derailed, ruptured, and spilled 20,000 gallons (about 197,000 lbs.) of ECH. The spill necessitated the evacuation of 400 people and the closing of the city's water plant (Anon., 1978a). The public water supply was from wells 25 feet deep but specific information on ECH concentrations, time for self-cleaning, or other details are not yet available (Rosencrance, 1978).

Other data on ECH release to the environment are much less quantitative. ECH has been detected in the following areas: air near a Russian factory (Fomin, 1966); air at a Russian glycerin plant (Lipina and Belyakov, 1975); air in a Russian pumping station where epoxy resins were used for waterproofing (Danilov and Muratova, 1972); and air in a Russian five-story dwelling which had used plastic materials for construction (Pinchuk et al., 1969).

Because of the reactivity of the epoxide ring, ECH released to the environment does not appear to be stable enough to be a widespread contaminant. Considerable information is available on the hydrolysis rates under varying conditions of pH and ion strength (Pritchard and Siddiqui, 1973; Bronstead et al., 1929; Le Noble and Duffy, 1964; Shvets and Aleksanyon, 1973; and Ross, 1962). Under environmental conditions, the half-life is likely to be between 4 and 8 days depending upon conditions. These hydrolysis studies also suggest that ECH or EBH may be formed from a number of precursors under basic conditions in water. Dilling and coworkers (1976) determined the decomposition rate of 10 ppm ECH in air containing 5 ppm nitric oxide and irradiated with sunlamps of intensity 2.6 times the intensity of Texas sunlight at noon in summer. The half-life was 16.0 hours. These reaction conditions simulate photochemical smog conditions, so the rates of decomposition under other conditions could be substantially longer.

No ambient monitoring studies that have been conducted so far have detected ECH or EBH in air, water, or soil samples. However, this may be due to the fact that no ambient monitoring work has been directed at detecting ECH or EBH.

The irritating properties of ECH to the eyes, skin, and respiratory tract of man have been recognized for many years (NIOSH, 1976b, 1977). Systematic absorption of ECH in man is known to occur, and has led to episodes of acute intoxication. Occupational exposure criteria have been developed by several agencies which are based primarily upon the irritating properties of ECH.

Recent studies have revealed, however, that ECH may produce adverse biological effects after chronic exposures in occupational situations. Cytogenetic damage, detected as chromosome abnormalities in peripheral lymphocytes, has been found in ECH-exposed workers in Czechoslovakia (Kucerova, 1977) and the United States (Anon. 1978a). These abnormalities may be taken as presumptive evidence of a carcinogenic/mutagenic threat to man, although their real significance and possible reversibility are not understood. Additional occupational morbidity studies (Pet'ko et al., 1966; NIOSH, 1976; Anon. 1978b) have failed to reveal alterations in a number of health parameters measured in ECH-exposed worker groups.

A recent examination of mortality among 864 active and retired workers exposed to ECH has revealed a statistically significant ($P<.05$) excess of deaths due to respiratory cancer (Enterline and Henderson, 1978). This report is the first to suggest that ECH may represent a carcinogenic threat to man. However, the lack of important data concerning exposure levels, pathology, and medical history prevents a definitive cancer risk assessment at this time.

The biological effects produced by ECH have been studied in numerous animal model systems. These investigations have provided not only important information which confirms observed effects in humans but also new data regarding mechanisms of toxic action. ECH is rapidly absorbed, widely distributed, and extensively metabolized in a manner which is consistent with other structurally-related chlorinated hydrocarbons (Weigel et al., 1978). One of the major metabolites of ECH in the rat is α-chlorohydrin; a compound known to have antifertility effects in the male (Jones et al., 1969; Cooper et al., 1974).

Studies with various animal species have established that ECH is highly irritating upon contact and moderately toxic by acute systemic absorption. The major organs adversely affected by acute exposures to ECH are the central nervous system, spleen, liver, respiratory tract, and the kidneys (Lawrence et al., 1972). The acute LD_{50} for ECH in the rat by oral administration is about 90-260 mg/kg (NIOSH, 1976b; Lawrence et al., 1972), and the LC_{50} (4-6 hour) for inhalation exposures is about 360-635 ppm (Synder, 1978; Grigorowa et al., 1974). The toxic effects produced and major target organs affected by repeated administration of ECH are similar to those for acute exposures (Fomin, 1966; Gage, 1959; Oser et al., 1975; Lawrence et al., 1972). However, several investigators reported hematologic disturbances with chronic exposures. In addition, the repeated oral administration of ECH to male rats produced a reversible sterility (Hahn, 1970; Cooper et al., 1974).

In several bacterial test systems, most notably the Ames assay, ECH was shown to be a direct-acting (i.e., without metabolic activation) mutagen (Elmore et al., 1976; Sram et al., 1976a,b). These positive results indicate that ECH may directly interact with DNA, and implicates ECH as a potential carcinogen/mutagen in higher organisms.

The potential carcinogenicity of ECH has been confirmed in animal bioassays. Among 140 rats inhaling ECH at 100 ppm (6 hours/day for 30 days), 13 died with squamous cell carcinomas of the nasal cavity (Nelson, 1978). Similar cancers were also produced in rats receiving lifetime exposures to ECH at a level of 30 ppm. It was concluded that, at least in occupational situations, ECH may present a potential risk to man.

There is very little information available regarding the effects of ECH on lower animals, plants, or microorganisms. Likewise, almost nothing is known concerning the biological activity of EBH.

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CONCLUSIONS AND RECOMMENDATIONS

From the preceding literature review and evaluation the following conclusions and recommendations seem justified.

1. Epichlorohydrin (ECH) is produced and used in large quantities (∿400 million lbs/year) and has considerable potential for environmental release.

2. Epibromohydrin (EBH) is insignificant commercially and should receive little if any attention.

3. Atmospheric release of ECH could amount to 600,000 lbs/year. Air monitoring data near production and use (glycerin and epoxy resin) plants are needed as well as in areas where substantial amounts of epoxy resins are used.

4. Substantial amounts of by-product waste (chloroethers, dichlorohydrins, and trichloropropanes) are generated during ECH production. The way in which this material is disposed of should be carefully examined.

5. ECH should be regarded as a potential carcinogenic threat to man in occupational situations. Further epidemiologic research is needed to confirm the existence of this hazard to man, and to evaluate the impact of ECH in community settings.

6. Additional experimental studies are required to more fully understand the potential hazards of ECH at low levels in the environment. Important data are lacking in the following areas: (a) pharmacokinetics and metabolism; (b) dose-response for toxicity and carcinogenicity; (c) *in vitro* bioassays for mutagenicity/carcinogenicity in mammalian cells; (d) effects on fertility; (e) reversibility of cytogenetic damage and ECH-induced sterility; and (f) effects on fish, invertebrates, wildlife, plants, and microorganisms.